AMERICAN HEART JOURNAL

June, 1960
Volume 59, No. 6

Editorial

Frank, Henderson, and Starling

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The editors of this journal deserve great credit for their willingness—in spite of the contemporary pressure for publication space—to give room for the printing of Otto Frank's pioneering and classic treatise which, translated, appears under the title, "On the Dynamics of Cardiac Muscle."[1] Even more credit is due to Dr. Chapman and Dr. Wasserman for their careful translation and their clarification of the text. This is a labor of love, well done. The word "clarification" is highly justified in referring to this translation, as one who has struggled with the original well realizes.

We will never know how much of Frank's approach was due to the influence of Ludwig, under whom he worked until a year before the publication of this treatise and a year before Ludwig's death. Ludwig gave physiology a tremendous stimulus. His influence was spread by his students all over the world, as far even as primitive Boston (Bowditch). Otto Frank could hardly have escaped the influence of this self-effacing master, for he was but 30 years old at the time of publication of this, his first major work.

The first few pages of the *Dynamics* consists of a detailed description of hydraulic arrangements and of his recording techniques. Recording techniques described here were hardly advanced beyond those of Hurthle. Later he gave manometry meticulous attention and developed the equations which enabled him to plan and construct his justly celebrated optical manometer in 1910. Although the details of Frank's manometer have been long superseded, the fundamental theory used in its design has been the basis of the hydraulics of the most sophisticated instruments in use today.

The relatively primitive methods of recording which were used in this research were adequate for the slow changes in pressure produced in the frog

Received for publication Nov. 20, 1959.

heart, and his proof of the fact that heart muscle follows the laws of skeletal muscle in that the tension developed in contraction increases with increased disatolic tension was very clear. He did not, however, explore that part of the diastolic tension-volume relationship in which the tension changes little with increased volume, and in which changes in volume (fiber length, as Starling showed much later) are of greater importance in controlling the performance of the heart than are changes in tension. He demonstrated that the decline in performance of the overfilled heart was often due to A-V regurgitation rather than to myocardial weakening—a possibility that has often been ignored by later workers.

In this paper, Frank recognized the fact that the heart works against aortic pressure only during systole (another thing that is often lost sight of now). Since he used rigid outflow tubes, no elastic storage of energy took place. The stroke volume then could be calculated, using Poiseuille's equation from the variations of ventricular pressure. In applying the pressure volume product in terms of the work done by the ventricle during systole, Frank insisted that the integrated products be used rather than the product of the stroke volume and the mean pressure. Later, according to Wiggers, he was to make this calculation by simple graphical methods, i.e., by measuring the area of a surface resulting from plotting the time course of pressure and change in volume against each other. He even devised an optical method of recording such a plot as a "vector loop."

In looking carefully at Frank's figures, one is led to speculate as to how he managed to record the ventricular pressure as maintaining itself at aortic levels after the incisura which Frank recognized as signaling closure of the aortic valves (see Figs. 15, 21, and 22 of the *Dynamics*), whereas it is usually seen to fall immediately to diastolic levels (Fig. 13 and all later work).

Frank seems to have been interested in the details of mechanisms rather than in fitting the mechanism into its function in relation to the operation of the animal as a whole. He proved beautifully that increased initial tension results in increased contractile tension, but it is difficult to find any hint in his writing that he attributes a functional significance to this mechanism as a compensating response to myocardial handicap or increased load. One wonders, in looking at Fig. 4, whether, among the many records which the industrious Otto made in preparing this series, there were not a number of tired weak hearts that would exert normal contractile tension at an abnormally high initial tension and, further, whether he would have seen the way in which functional inadequacy could produce the increase in initial tension that would in turn produce the essential feedback. It is this insight that has made "The Law of the Heart" the significant generalization which it has long been recognized to be. Frank did not see, as Henderson and, later, Starling did, that he was dealing with the makings of a self-governing mechanism. He may have been imbued with nineteenth century mechanistic philosophy that shunned what seemed teleologic or vitalistic, nor was the time ripe to think much about the Darwinian evolution of adaptive mechanisms that seem on the surface to be teleologic, but which are really based on natural law. This area between philosophy and science was not for Frank. The field which he made his, and in which he left such "descendants" as

Bromser, Wetzler, Wetterer, and our own Wiggers, was ingenious instrumentation, the meticulous recording of hemodynamic phenomena, and the mathematical analyses of their details.

This contribution which has been so admirably translated for these pages showed the application to the heart of the laws which had been worked out for skeletal muscle by Fick and Blix. It is essentially a masterful study of a phase of cardiac muscle physiology and it opened the way for the imaginative syntheses of Yandell Henderson and Ernest Starling.

Henderson was concerned with the maintenance of a constant blood volume in the lungs and writes in 1914,[2] "The experiments here reported show the controlling influence of the diastolic distending pressures in the ventricles upon their tidal volumes. The results indicate that the volume of blood in the lungs must be in great part regulated by the relative efficiency of the two sides of the heart.

"The right ventricle (of the cat's heart) reaches its greatest tidal volume at the 'critical' pressure of about 50 mm. saline. As this is approximately the effective pressure (i.e., the absolute venous pressure plus intra-pleural negative pressure) maintained during life, the conclusion is drawn that the right ventricle normally works at maximum efficiency.

"The left ventricle at pressures below 50 mm. saline has a much smaller stroke than the right. During life this function of the left ventricle prevents pulmonary depletion. Between 50 mm. and 80 mm. the two ventricles have about equal tidal volumes, and the volume of blood in the lungs therefore would be maintained at a nearly constant point. At higher pressures, the tidal volume of the left ventricle continues to increase up to a limit which is probably above any which occurs normally. This ability of the left ventricle, under high pressures in the lungs, to pump more than the right is the function which normally prevents pulmonary congestion."

In 1914, Starling, working with Patterson, Piper, Evans, and others, published a series of searching investigations which described the manner in which the heart, bereft of all hormonal, or reflex, controls would respond to the challenge of increased arterial pressure or increased venous return. Each of these challenges caused the heart to retain residual blood at the end of systole until the heart dilated in sufficient measure so as to beat strongly enough to meet the challenge—to do the required work against the increased arterial pressure or to pump out the increased venous return as fast as it came to the heart. Starling described a delightfully simple and elegant example of what now might be called cybernetics, in which failure of the heart to perform its task leads automatically to increased cardiac size, which, in turn, leads to a greater measure of work until a new balance is struck fitting the new task.

Starling's researches were not concerned with hormonal and reflex control of cardiac function which were well known to all physiologists at that time. These controls were purposely ruled out by his experimental design. Reflex and hormonal controls and the patterns of cardiovascular activity as set by the higher centers are under study at the present time, but one can venture the guess that the role of the response of muscle to stretching as we learn it from Fick, Blix, and Frank

and as it was given a functional meaning in the living animal by Henderson and Starling will always be a fundamental background for our understanding.

In conclusion, may I quote a final passage from Starling's Linacre Lecture[3] which is good for the spirit of all who dwell in ivory towers.

"The connection which I have shown in this lecture to exist between the energy of the heart's contraction and the length of its muscle fibres, enables us to understand not only the marvellous power of adaptation of the heart to the varying strains of everyday life, but also the condition of this organ in disease, when from overstrain or morbid alterations in its muscles or its valves it fails to carry on its functions with efficiency.

"For years the 'muscle-nerve physiologist' was reproached by the so-called practical man with spending his time and attention on things which can have little importance in medicine, for the maintenance of health or the cure of disease. And yet it is in the researches on a subject, considered even by some physiologists as wearisome or trivial, that we have found the clue to the behaviour of the heart under all manner of conditions, and the explanation of phenomena which have long been a puzzle to the student of the healthy or diseased organism. But however plodding the mode of attack may have appeared, there was nothing trivial in the goal to which Blix's researches were directed, since this was nothing less than the essential nature of the contractile process: they were to bring within the scope of known categories of phenomena the mysterious (*vis insita*) of muscle, which to the older physiologists, and indeed to ourselves, is a type or a part of life itself. In physiology, as in all other sciences, no discovery is useless, no curiosity misplaced or too ambitious, and we may be certain that every advance achieved in the quest of pure knowledge will sooner or later play its part in the service of man."

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Clinical Communications

The Sounds at the Base of the Heart in Cases of Patent Ductus Arteriosus

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For a number of years we have observed certain peculiarities of the heart sounds along the upper left sternal border in cases of patent ductus arteriosus with large left-to-right shunts. The present study consists of phonocardiographic and auscultatory findings and certain physiologic correlations in 30 patients with patent ductus arteriosus. The phenomena given particular attention in this study were the early systolic ejection sounds of aortic and pulmonic origin and a midsystolic ejection sound probably of pulmonic origin, paradoxical splitting of the second heart sounds, and a group of sounds in late systole and early diastole which have recently been given the designation, "eddy sounds," by Neill and Mounsey.[1]

MATERIALS AND METHODS

The data were obtained from 30 patients with patent ductus arteriosus on whom at least one phonocardiographic study and routine right heart catheterization had been performed. Ten of the patients had simultaneous right heart catheterization and phonocardiography. Twelve of the patients had simultaneous direct puncture aortic and pulmonary pressure records with direct surface phonocardiography from the great vessels at the time of surgery. The phonocardiograms were obtained with either a Sanborn Twin-Beam phonocardiograph, an Electronics for Medicine recorder, or a specially constructed phonocardiographic amplifier-recorder with a continuously variable selective band-pass filter. The patients ranged in age from 3 months to 50 years; 7 of the patients were less than 1 year of age.

Six of the patients had left-to-right shunts of less than 30 per cent of the total pulmonary flow, and the remainder of the patients had left-to-right shunts of from 40 to 80 per cent of the total pulmonary flow. None of the patients had right-to-left shunts. In none of these patients was the pulmonary vascular resistance greater than 60 per cent of the systemic resistance.

RESULTS

All but 5 patients in the group, all under 3 years of age, showed typical continuous murmurs. The 6 patients with shunts of less than 30 per cent exhibited

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Supported in part by grants from the Nebraska Heart Association and the U. S. Public Health Service.

Received for publication Nov. 16, 1959.

none of the abnormalities of the heart sounds described below, and the following discussion refers to the patients with the larger shunts unless otherwise specified.

Systolic Ejection Sounds.—All but two of the patients with large shunts showed at least a single systolic ejection sound occurring from 0.07 to 0.16 second after the onset of the first heart sound (Fig. 6,*B*). When this sound was single, it was usually maximal along the mid-left sternal border at end expiration.

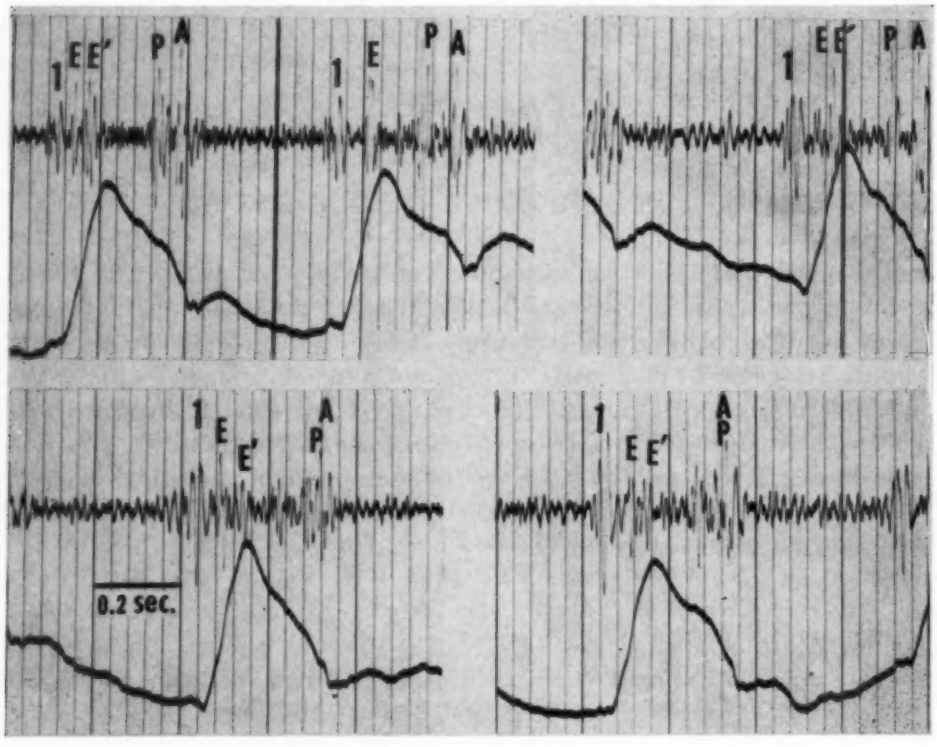

Fig. 1.—Stethoscopic phonocardiograms recorded from the third intercostal space at the left sternal margin and carotid pulse. The tracing shows early systolic ejection sounds of both pulmonic and aortic origin. There is also paradoxical splitting of the second sound. The patient had a patent ductus arteriosus with a left-to-right shunt equal to 70 per cent of the total pulmonary flow and normal pulmonary arterial pressures. *P:* Pulmonic second sound. *A:* Aortic second sound. *E:* Pulmonic ejection sound. *E':* Aortic ejection sound.

When the ejection sound was single, it was usually of pulmonary arterial origin and corresponded to a notch on the upstroke of the pulmonary arterial pressure curve. In a few of these a superimposed sound related to aortic ejection could not be excluded. In 10 of the patients, all with shunts in excess of 50 per cent of the total pulmonary flow, two early ejection sounds separated by an interval of from 0.03 to 0.08 second were detected (Fig. 1). Six of these patients had simultaneous direct-puncture aortic and pulmonic pressures and surface phonocardiograms from the aorta and pulmonary artery. It was established that the pulmonic ejection sound preceded the aortic in all but one patient with a very large shunt and pulmonary arterial pressures equal to the systemic. From simultaneous phonocardiography and cardiac catheterization, the aortic ejection

sound was found to vary considerably in intensity but little in timing from cycle to cycle. The pulmonic ejection sound became more intense and occurred later with expiration. However, both sounds could vary spontaneously in timing and intensity without any consistent relationship to an identifiable hemodynamic change. In 5 of these patients, all with large shunts and elevated pulmonary artery pressures, an additional sound in midsystole corresponded to the arrival of the aortic pressure peak at the ductus (Figs. 2-4). The loudest ejection sounds were in general associated with the largest shunts and/or the greatest degree of dilatation of the pulmonary trunk.

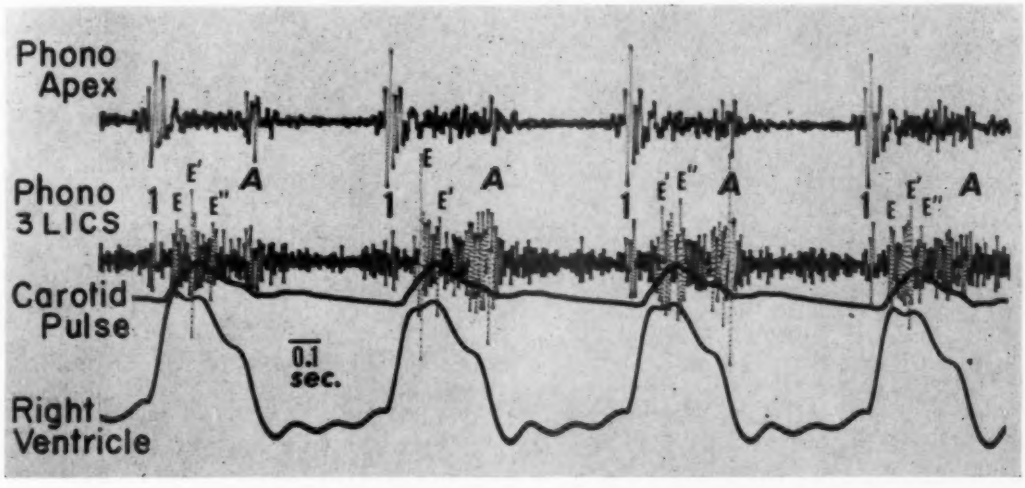

Fig. 2.—Phonocardiograms from the apex (20 to 200 cycles/sec.) and from the third left intercostal space (40 to 200 cycles/sec.) at the time of cardiac catheterization. The phonocardiogram recorded from the third intercostal space shows an early pulmonic ejection sound, an early aortic ejection sound, and a later ejection sound of pulmonic origin. The patient had a patent ductus arteriosus with a left-to-right shunt equal to 55 per cent of the total pulmonary flow and normal pulmonary arterial pressure. *E:* Early pulmonic ejection sound. *E':* Aortic ejection sound. *E":* Late pulmonic ejection sound. *A:* Aortic second sound.

Paradoxical Splitting of the Second Sound.—Sixteen of the patients with large shunts exhibited at least some degree of paradoxical splitting of the second sound along the mid-left sternal margin. In general, the patients with the largest shunts showed the greatest degree of paradoxical splitting. Of the patients with large shunts who did not show the phenomenon, five were below 5 years of age.

In the mildest form the aortic sound coincided with or preceded the pulmonic sound on inspiration and followed the pulmonic sound on expiration. In more advanced forms the pulmonic sound always preceded the aortic sound (Figs. 1 and 5). The interval from pulmonic to aortic sound varied from 0.02 to 0.14 second.

It was not possible to study paradoxical splitting with the chest open, as the sounds tended to become superimposed. However, by comparison of the aortic and pulmonic pressure curves immediately before and after closure of the ductus in 10 patients with large shunts, it was found that the change in the interval from Q on the electrocardiogram to the aortic dicrotic notch was variable, but

Q to pulmonic dicrotic always increased after closure of the ductus. In the phonocardiograms and right heart catheterization studies it was shown that the respiratory variation in the degree of splitting was primarily dependent on variation in the duration of right ventricular ejection. It was observed that there was considerable spontaneous variation in the intensity and degree of splitting of the second sound without relation to the respiratory cycle or any other identifiable event.

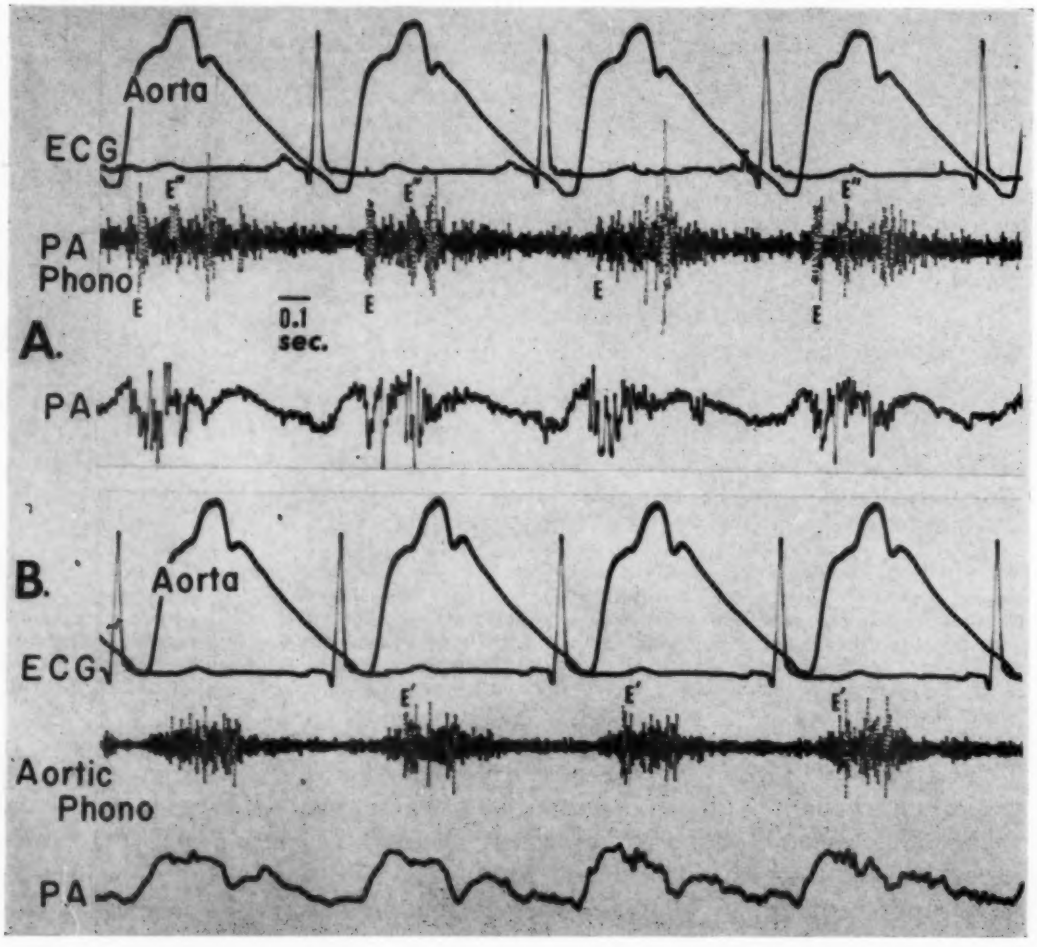

Fig. 3.—Direct surface phonocardiograms (40 to 200 cycles/sec.) from the pulmonary artery (*A*) and aorta (*B*) recorded at the time of operation. There are simultaneous direct-puncture pressure recordings from the pulmonary trunk and aorta just opposite the ductus. In *A* the pressures are unfiltered. An early and late systolic ejection sound are recorded from the pulmonary trunk. An ejection sound of intermediate timing is recorded from the aorta. *E:* Early pulmonic ejection sound. *E":* Late pulmonic ejection sound. *E':* Aortic ejection sound.

Eddy Sounds.—In 15 patients, all with shunts in excess of 50 per cent of the total pulmonary flow, additional sounds in late systole and early diastole could be identified in some cycles (Figs. 6 and 7). These sounds occurred with different timing from cycle to cycle but tended to be grouped from 0.16 second before

to 0.12 second after the aortic sound, and their distribution in the cycle corresponded to the peak of the aortic-pulmonary gradient across the ductus. As many as five of these sounds could be identified in a cycle, although they were often absent in many consecutive cycles. They could be recorded with maximum intensity from the pulmonary trunk and left main pulmonary artery and had their apparent equivalent in high-frequency spikes on the direct needle puncture pressure recording from the pulmonary artery just opposite the ductus. They bore no apparent relationship to the respiratory cycle or body position. They were usually best detected on recording somewhat medial to the area of maximum intensity of the continuous murmur.

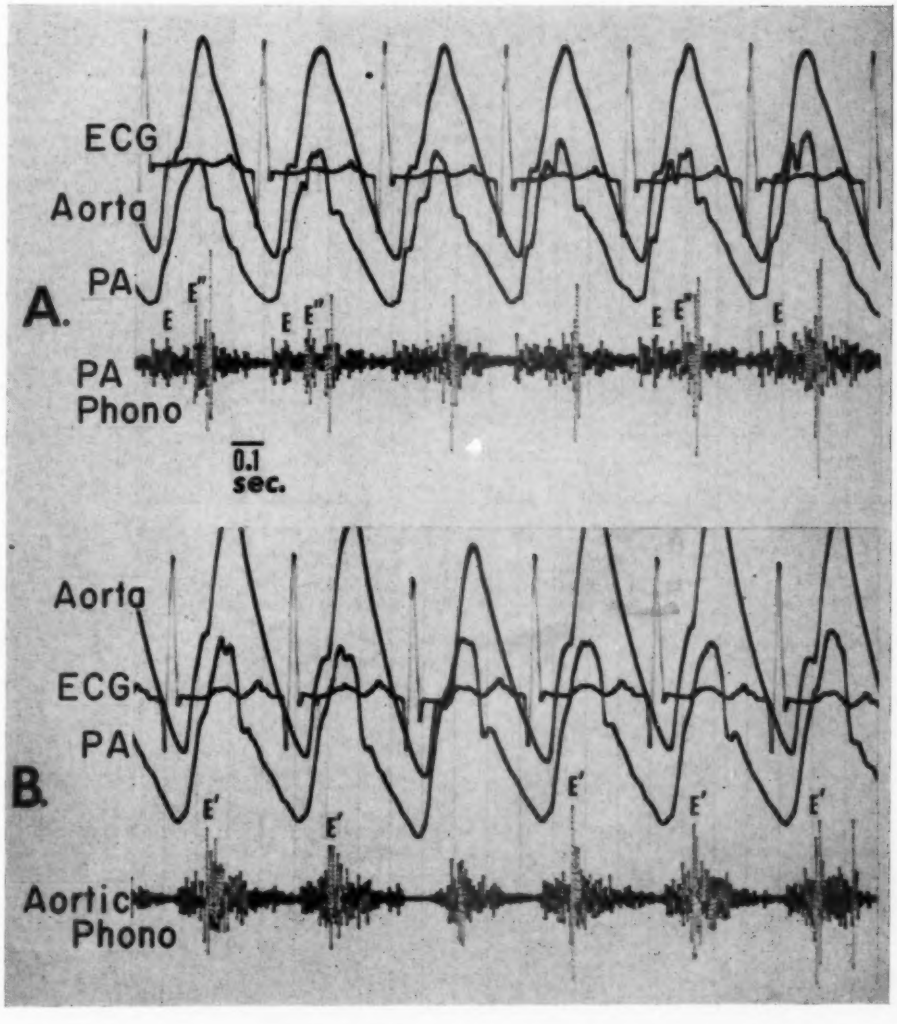

Fig. 4.—Direct surface phonocardiograms (40 to 200 cycles/sec.) from the pulmonary artery (*A*) and aorta (*B*). There are simultaneous direct-puncture pressure recordings from the pulmonary trunk and aorta just opposite the ductus. The aortic phonocardiogram is recorded at twice the sensitivity of the pulmonic recording. There is an early and a late ejection sound recorded from the pulmonary artery and an ejection sound of intermediate timing recorded from the aorta. *E:* Early pulmonic ejectino sound. *E':* Aortic ejection sound. *E'':* Late pulmonic ejection sound.

DISCUSSION

Ejection sounds and their mechanisms have been well described.[2,3] In patent ductus arteriosus with large left-to-right shunt, high stroke output into the proximal aorta and right ventricular ejection into a dilated pulmonary artery are circumstances which may produce ejection sounds of either pulmonic or aortic origin or both. It was possible in some of the patients to determine the origin of the ejection sound by its correspondence to a notch on the upstroke of the respective arterial pulse wave or by direct surface phonocardiography. A single ejection sound was usually of pulmonic origin. When double, the pulmonic sound preceded except in one patient with major pulmonary hypertension. In a few patients a later ejection sound corresponded to the arrival of the peak of the aortic pulse wave at the ductus and may have been due to sudden further distention of the pulmonary artery.

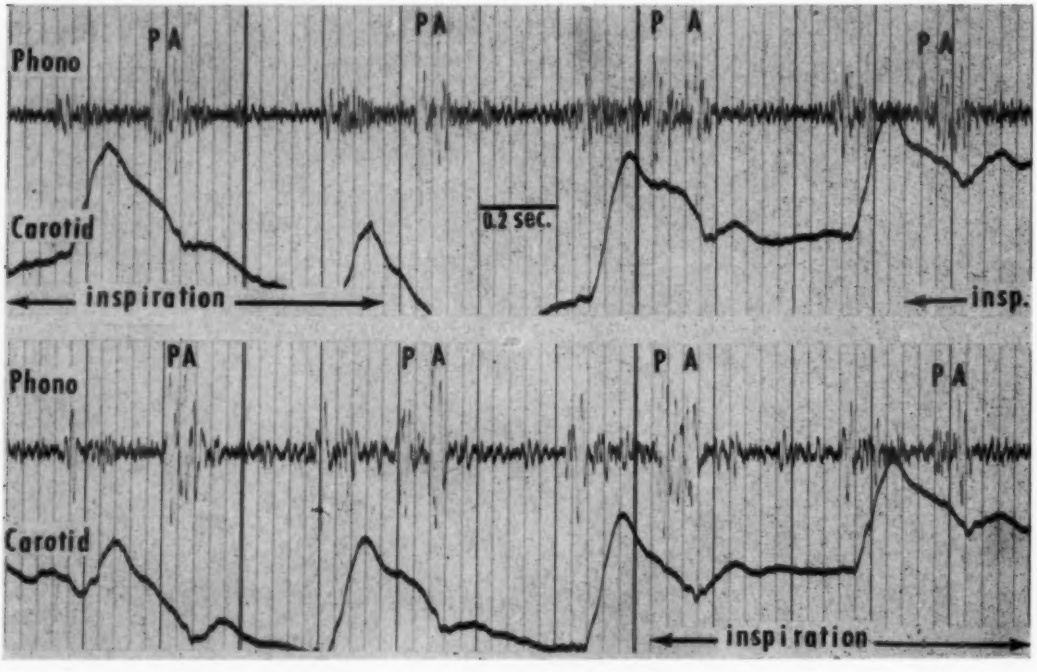

Fig. 5.—Phonocardiogram recorded from the third intercostal space at the left sternal margin, and piezoelectric carotid pulse tracing. The pulmonic second sound precedes the aortic second sound throughout the respiratory cycle, and the degree of splitting decreases with inspiration. The patient had a left-to-right shunt equal to 70 per cent of the total pulmonary flow and normal pulmonary arterial pressures. *P:* Pulmonic second sound. *A:* Aortic second sound.

Paradoxical splitting of the second sound in patent ductus arteriosus has been described by Gray.[4] He attributed this to respective prolongation and shortening of left and right ventricular ejection. In our studies of the aortic and pulmonic dicrotic notch before and after closure of the ductus, there was always prolongation of pulmonic ejection after closure of a large ductus, whereas there was no consistent effect on aortic closure. Similarly, most of the respiratory variation

in splitting was due to variation in the duration of pulmonic ejection and was generally longest with decreasing pulmonary pressure on inspiration.

An account of the high-frequency sounds in the pulmonary area occurring in late systole and early diastole in patent ductus arteriosus has been presented by Neill and Mounsey.[1] They referred to these as "eddy sounds" and attributed them to the turbulence from "head-on" collision of streams from the ductus and pulmonary artery. The sounds tended to be distributed randomly within a short period about the aortic second sound, corresponding to the period of peak flow in the ductus and often occurring after the termination of right ventricular ejection. It is likely that they represent sounds produced in some manner by the crossing streams of flows of the ductus and left pulmonary artery, or possibly transients which originated from the jet of the ductus striking the wall of the left pulmonary artery.

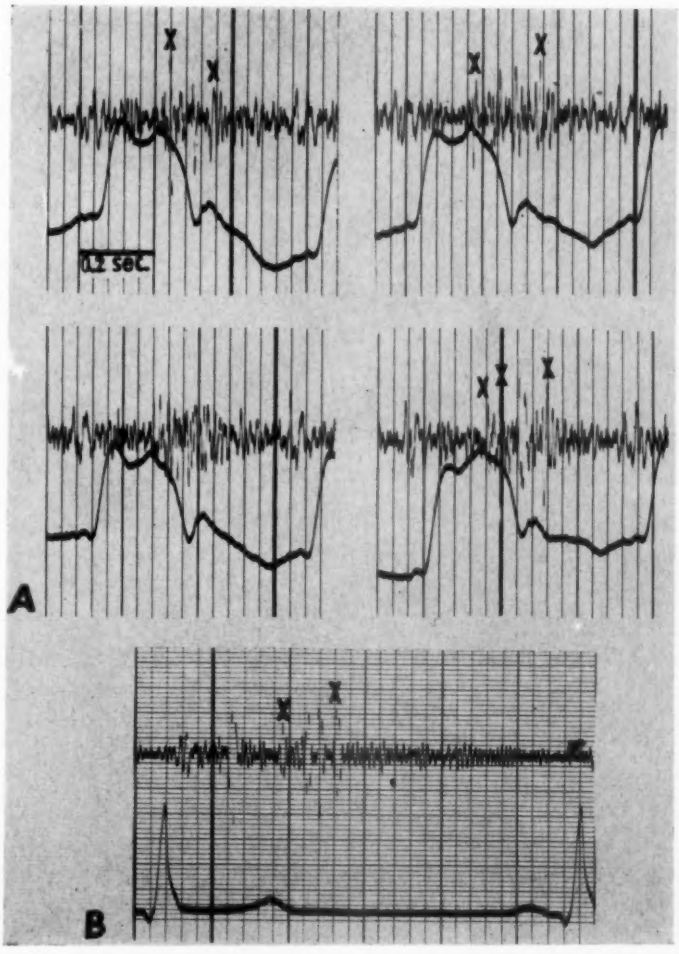

Fig. 6.—*A*, Stethoscopic phonocardiogram recorded from the third intercostal space at the left sternal margin, and piezoelectric carotid pulse tracing. Four different cycles show the variable occurrence and timing of the "eddy" sounds about the aortic second sound. *B*, Logarithmic phonocardiogram from the third left intercostal space and Lead III of the electrocardiogram. There are eddy sounds before and after a split second sound. There is an ejection sound in early systole. *X:* Eddy sounds.

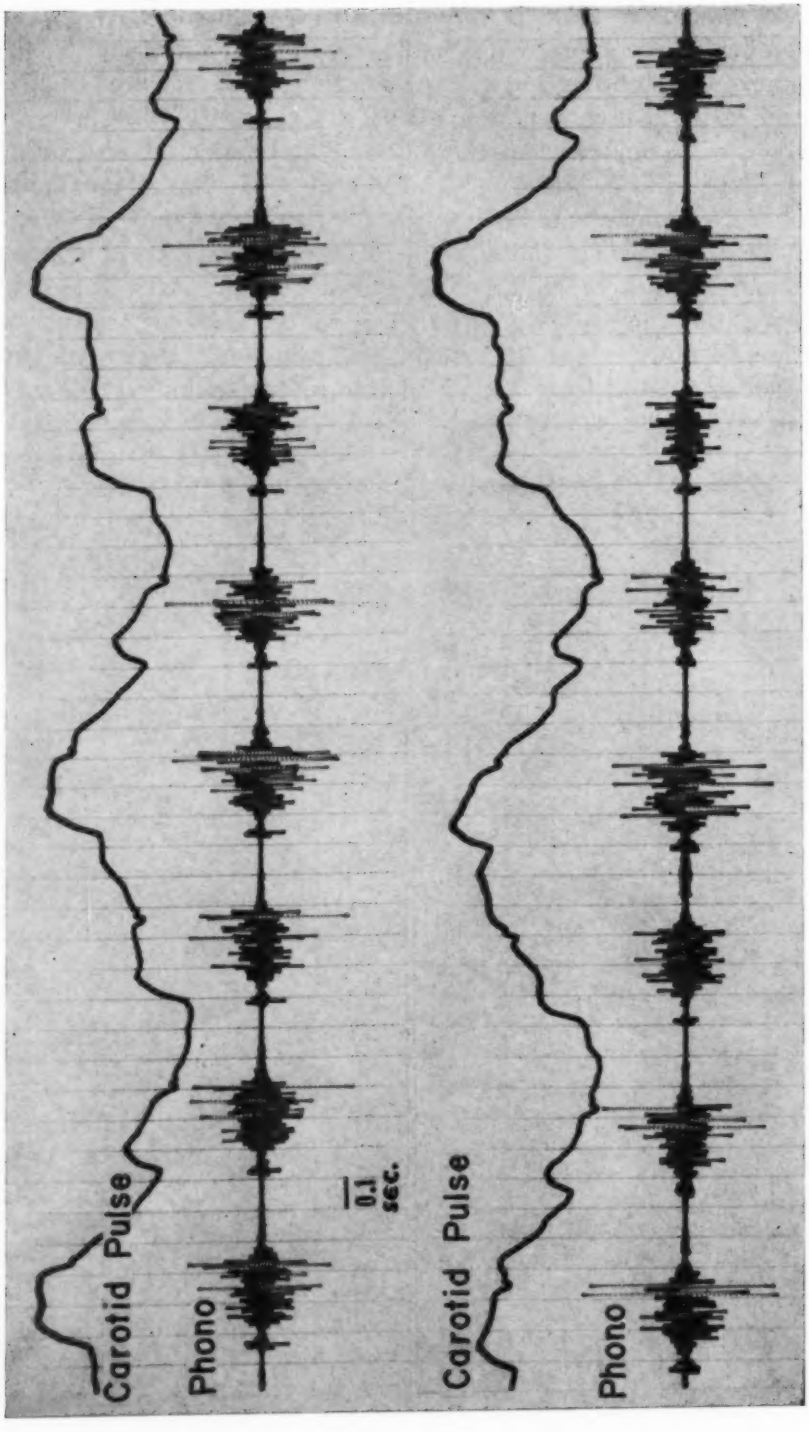

Fig. 7.—Phonocardiogram (40 to 200 cycles/sec.) recorded from the mid-left sternal margin, and a carotid pulse tracing from a 4-month-old infant. Although the murmur is not typical of patent ductus, various cycles exhibit pulmonic and aortic ejection sounds, "eddy" sounds, and slight paradoxical splitting of the second sound.

Since most patients with patent ductus arteriosus are operated upon without cardiac catheterization or other special studies, the clinical significance of these sounds lies in their value in differential diagnosis of continuous murmurs and as an aid in the evaluation of the severity of the dynamic abnormality. The auscultatory identification of the aforementioned sounds in the presence of the continuous murmur may at times be difficult; however, awareness of their occurrence, their characteristic location, and the effects of respiratory maneuvers usually allows proper assessment.

The single systolic ejection sound is usually indicative of some dilatation of the pulmonary trunk, and double or triple ejection sounds are always associated with large left-to-right shunts. The degree of paradoxical splitting of the second sound is a rough guide to the volume of left-to-right shunt in older children and adults; this phenomenon is less consistent in infants and small children. The presence of well-defined eddy sounds is associated with the largest shunt volumes. These phenomena in association with the familiar mid-diastolic apical murmur indicated a very substantial left-to-right shunt. Normal splitting of the second sound with a normal respiratory effect in a patient over 12 years of age will usually indicate a small to moderate shunt.

By observation of the aforementioned sounds, we have repeatedly been able to make the diagnosis of patent ductus arteriosus in infants and small children in the absence of typical characteristics of the murmur (Fig. 7). Of the several lesions which cause continuous murmurs, only aortic-pulmonary window might be expected to produce at least a double ejection sound and paradoxical splitting. Of 2 patients studied with aortic-pulmonary window, both had single pulmonic ejection sounds, and 1 presented questionable paradoxical splitting of the second sound.

SUMMARY

A study has been made of the mechanism of production and significance of some abnormalities of the sounds at the base of the heart in cases of patent ductus arteriosus. These included early systolic ejection sounds of pulmonic and aortic origin, paradoxical splitting of the second sounds, and high-frequency sounds occurring irregularly in late systole and early diastole.

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Transposition Functionally Totally Corrected, Associated With "Mitral" Insufficiency

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INTRODUCTION

Mitral insufficiency caused by congenital heart malformations is a rather rare condition in comparison with that caused by rheumatic heart disease. The following types of such malformations are described in the literature[15,16,30,50]: (1) persistent common atrioventricular canal with a cleft in the anterior mitral leaflet; (2) double orifice of the mitral valve, consisting of an extra opening in one of the cusps, or a cleft in the anterior mitral cusp; (3) aplasia or malformation of a mitral leaflet or chordae tendineae; (4) ventricular septal defect with a large left-to-right shunt, dilated left ventricle, and secondary annular enlargement; (5) anomalous chordal insertion, often in association with ventricular septal defect, altering the normal closure of the mitral cusps—a special variety occurs in corrected transposition of the great vessels (henceforth named "corrected transposition"); (6) a complex valvular malformation, which has similarity to Ebstein's malformation, in association with corrected transposition—the "mitral" valve is in this form tricuspid and a concomitant "mitral" stenosis is sometimes present; (7) endocardial fibroelastosis affecting both left ventricle and chordae tendineae, and possibly pseudoxanthoma elasticum affecting endocardium and mitral valve.[11]

Recently, at the University Hospital of Uppsala, we have had the opportunity to study clinically one case of "mitral" insufficiency associated with corrected transposition but without the usual association with defects causing shunt. Thus, our case is one of the extremely rare cases of functionally totally corrected transposition with "mitral" insufficiency hitherto diagnosed in vivo.

ANATOMIC FEATURES OF CORRECTED TRANSPOSITION

Much has been written on the subject of transposition of the great vessels as well as corrected transposition, with no general agreement as to their embryo-

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Received for publication Nov. 13, 1959.

logic basis. Transposition is involved as the anteroposterior relationship of the great vessels is reversed. Likewise, inversion is involved, which means that an organ (or part of an organ) is formed as a mirror-image of the normal, with alteration of left and right relationship. Since von Rokitansky,[38] in 1875, published a comprehensive work of the pathogenesis of cardiac anomalies, based directly on embryologic studies, many other authors have made similar careful studies without getting general acceptance of their theories.[12,26,33,34,40,42,48]

Corrected transposition means that the serious hemodynamic disturbance of complete (or "uncorrected") transposition of the great vessels, wherein the

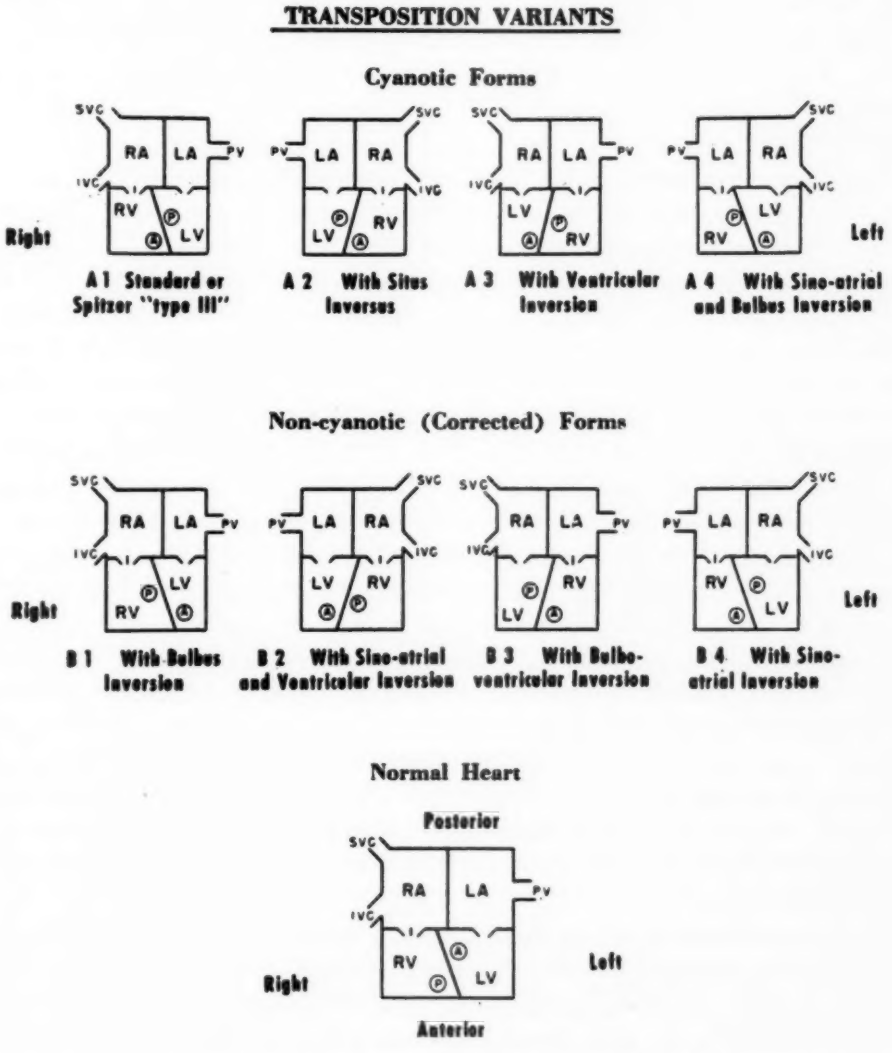


Fig. 1.—Transposition variants after Harris and Farber,[26] Cardell,[9] and Anderson and associates.[2] The abbreviations are as follows: *SVC*, Superior vena cava. *IVC*, Inferior vena cava. *RA*, Right atrium. *LA*, Left atrium. *PV*, Pulmonary veins. *RV*, Anatomic right ventricle. *LV*, Anatomic left ventricle. *P*, Pulmonary artery. *A*, Aorta. The three-cusped valve is indicated by three lines, and the two-cusped atrioventricular valve by two lines. Note the different relationships of the ventricular septum to the atria. Normal heart is shown for comparison. (From Anderson, Lillehei, and Lester, *Pediatrics* 20:626, 1957.)

aorta contains unoxygenated, and the pulmonary artery oxygenated, blood, is corrected. In corrected transposition the aorta receives oxygenated, the pulmonary artery unoxygenated, blood (at least in comparison). The external anatomic abnormality of the great vessels in this condition consists in the aorta lying in front and to the left (in a few cases to the right) of the pulmonary artery, and running parallelly, they do not cross each other as in a normal heart.

To visualize the differences between the complete transposition and the corrected transposition, on the one hand, and schematically to show the different types of corrected transposition, on the other, we are reproducing a scheme of transposition variants after Harris and Farber,[26] Cardell,[9] and Anderson and associates[2] (see Fig. 1). Thus, there are four basic types of corrected transposition: (1) Type B 1, with bulbus inversion; (2) Type B 2, with sinoatrial and ventricular inversion; (3) Type B 3, with bulboventricular inversion; (4) Type B 4, with sinoatrial inversion.

The form with bulboventricular inversion is most common. In this form the right-sided ventricle with the anomalously passing pulmonary artery has the morphologic features of a normal left ventricle (without conus and its septal surface is only slightly trabeculated, without papillary muscles) and vice versa. The right atrioventricular valve has the appearance of the mitral valve, with two leaflets, and the left atrioventricular valve has the appearance of the tricuspid valve, with three leaflets. (Therefore, in this connection, the word mitral is set off in quotation marks.) Frequently, there is also inversion and/or transposition of the coronary arteries: they both arise from the aorta. Single coronary artery is also described in 1 case by Lev.[31] Besides, in 1914, Sato[40] described 1 case with transposition of the bundle of His.

As a rule, corrected transposition is associated with other cardiac malformations, most often ventricular septal defect. In this connection, other defects causing shunt have been reported as patent ductus arteriosus and atrial septal defect. Also, pulmonary stenosis, coarctation of the aorta, and malformations of the left atrioventricular valve may occur. Various combinations of these other malformations are also described in association with corrected transposition. Besides, Carns and Ritchie,[10] in 1941, described 1 case associated with a hypoplastic and calcified aorta (and ventricular septal defect), and Espino-Vela and associates[17] reported 1 case with a hypoplastic pulmonary artery with its right branch exhibiting distal narrowing (and ventricular septal defect and valvular pulmonary stenosis).

Anomalies of the vessels arising from the aortic arch are also reported. Von Rokitansky[38] described a case of corrected transposition in which the left vertebral artery arose from the aortic arch directly, and Walmsley[48] had a similar case with a common stem for the right brachiocephalic trunk and the left common carotid artery.

There are, however, some cases of corrected transposition without other cardiac malformations. In 1955, Platzer,[37] reporting 2 cases of that type, termed them *functionally totally corrected transpositions*. In our opinion, the term may be widened to comprise all of the cases of corrected transposition without defects

causing shunt. Thus, those associated with pulmonary stenosis, coarctation of the aorta, and malformation of the left atrioventricular valve belong to this group.

The rarity of extracardiac congenital malformation associated with complete transposition has been emphasized by Wiland.[49] Liebow and McFarland,[33] in 1941, described 1 case of corrected transposition with stenosis of the ureters, and in 1958, Kernen[29] reported 1 case with stenosis of one ureter.

REVIEW OF THE CASES IN THE LITERATURE

Corrected transposition was first described by von Rokitansky[38] in 1875. In 1956, Cardell[9] reviewed 24 cases, describing 1 of his own of corrected transposition. Our review of the literature revealed 74 cases. According to the definition of corrected transposition mentioned previously in this paper by us, and pointed out by Cardell,[9] it seems better to restrict the use of the term "corrected transposition" to cases of functionally corrected complete transposition, i.e., cases in which the aorta receives oxygenated blood. Therefore, we have not accepted some other cases because of associated lesions, such as complete atresia of the left atrioventricular valve with ventricular septal defect (Donoso and associates[14]), atresia of the same valve with ventricular and atrial septal defect (Anderson and associates[2]), and common atrioventricular valve with ostium atrioventriculare commune (Espino-Vela and associates,[17] 1959, Case 1). These associated malformations gravely impair the functional correction.

Of the 74 cases recorded by us, corrected transposition is the only abnormality in 6 cases, whereas information of possibly associated lesions is lacking in 4 cases. The various combinations of the malformations in the remaining 64 cases are listed in Table I. From this table it may be seen that the most often associated cardiac malformation is ventricular septal defect, which is present in 48 cases. Other defects as the only cause of shunt are present in 5 cases. The remaining 11 cases associated with other cardiac malformations are classified as functionally totally corrected transpositions. If the 6 cases of corrected transposition without other cardiac malformation are added, there are 17 cases belonging to this totally corrected group (see Table II).

The anatomic types of corrected transposition are recorded in 44 cases, and there are 19 probable cases. This information is not recorded in 11 cases. The form with bulboventricular inversion (B 3) is by far the most common, i.e., 33 cases are of that type. (Anderson[2] has reported 19 further probable cases.) Bulbus inversion (B 1) is met with in 6 cases, sinoatrial inversion (B 4) in 3 cases, and sinoatrial and ventricular inversion (B 2) in 2 cases. Inversion and transposition of the coronary arteries is found in at least 20 cases, in those in which it can be recorded.

SEX AND INCIDENCE

There are 56 cases in the literature in which the information of sex is given. The sexes are equally represented, 29 males and 27 females. The incidence of complete transposition of the great vessels is, according to Gasul and associates,[20]

4.2 per cent of all congenital heart malformations. The incidence of corrected transposition is 0.6 per cent, according to Abbott,[1] her figures originating from only postmortem examinations. The incidence of corrected transposition is surely considerably higher than the number of reported cases would seem to indicate. The condition has probably been overlooked, as an increasing number of cases in the literature during the last few years will demonstrate.

TABLE I. CORRECTED TRANSPOSITION WITH ASSOCIATED CARDIAC MALFORMATIONS (64 CASES)*

	ONLY	VSD	PDA	VSD + PDA	VSD + CA
VSD	25	—	–	–	–
PDA	2	2	–	–	–
ASD	1	—	–	–	–
PS	5	10	–	2	–
CA	2	2	1	–	–
MI	3	4	1	–	1
MS	1	1	1 (+CA)	–	–

*Total of 74 cases, of which information is lacking in 4 cases. Corrected transposition as the only abnormality was encountered in 6 cases.

VSD: Ventricular septal defect. PDA: Patent ductus arteriosus. ASD: Atrial septal defect. PS: Pulmonary stenosis. CA: Coarctation of the aorta. MI: "Mitral" insufficiency. MS: "Mitral" stenosis.

PHYSICAL FINDINGS

The physical findings in corrected transposition depend partly on the type of associated malformation. On the other hand, the presence of corrected transposition may cause the physical findings of these malformations to become atypical. For example, Anderson and associates,[2] publishing a survey of the clinical findings in 17 cases of corrected transposition in 1957, noted in 4 cases associated with pulmonary stenosis that the aortic second heart sound was louder below the left clavicle than below the right, the reverse of that usually found in pulmonary stenosis. This is explained by the anomalous position of the systemic aorta, which causes the aortic second sound to be heard best at the left sternal edge. The position of the punctum maximum of murmurs and thrills was also atypical in these cases.

ELECTROCARDIOGRAPHIC FINDINGS

Walmsley,[48] in 1931, was the first to describe the ECG finding of a complete atrioventricular block in a patient with corrected transposition as the only abnormality. Walmsley attributed the atrioventricular block to fibrosis of the bundle of His. Since then, 9 further cases of complete atrioventricular block, 5 cases of atrioventricular block of second degree (usually 2:1 block), and 3 cases of first degree block have been recorded. Moreover, there are 2 cases of atrioventricular dissociation. Anderson and associates[2] found in their series a reversal of the usual precordial pattern of rS in Lead V_1 and qR in Lead V_6 corresponding to the inversion of the ventricles. Other fairly constant findings were high voltage of the P waves in Lead II, widening of the QRS complex, and T waves becoming

positive in Lead V_{4R} and continuing across the precordium to Lead V_6. When a complete A-V block or A-V dissociation, or nearly all of the other mentioned ECG findings are present, the diagnosis of corrected transposition should be considered, according to Anderson and associates.[2]

The electrocardiographic pattern depends partly on the hypertrophy caused by possibly associated malformation, and partly on the positions of the various chambers of the heart in the thorax. Both factors vary considerably.

TABLE II. FUNCTIONALLY TOTALLY CORRECTED TRANSPOSITION (17 CASES)

CASE NUMBER	AUTHOR, YEAR	AGE (YR.)	SEX	ASSOCIATED DEFECTS	TYPE	DIAGNOSED BY	NOTES
1.	Graanboom, 1891	33	M	—	B 3	Autopsy	Dead in renal disease
2.	Sato, 1914	?	?	CA	B 3	Autopsy	—
3.	Walmsley, 1931	35	M	—	B 3	Autopsy	Complete A-V block Cardiac failure
4.	Roos, 1936	8/12	F	CA	B 3	Autopsy	Complete A-V block
5.	Edwards, 1954	60	M	—	B 3	Autopsy	Dead in peritonitis
6.	Edwards, 1954	31	F	"MI"	B 3	Autopsy	—
7.	Platzer, 1955	"Grown up"	?	—	B 3	Autopsy	—
8.	Platzer, 1955	26	F	—	B 4	Autopsy	Dead in tuberculous meningitis
9.	Helmholz, 1956	17	F	"MI"	?	Cardiac catheterization	Alive
10.	Gibbons, 1956	?	?	PS	?	Surgery	?
11.	Gibbons, 1956	?	?	PS	?	Surgery	?
12.	Anderson, 1957	16	M	"MS"	?	Cardiac catheterization	A-V dissociation. Alive
13.	Anderson, 1957	11	M	PS	B 3(?)	Surgery	Alive
14.	Anderson, 1957	12	M	PS	B 3(?)	Surgery. Angiocardiography	Alive
15.	Anderson, 1957	11	M	PS	B 3(?)	Surgery	A-V dissociation. Alive
16.	Schaefer, 1957	36	F	—	B 3	Autopsy	Complete A-V block Dead in heart failure
17.	Kjellberg, 1959	13	F	MI	B 3	Angiocardiography	Incomplete A-V block

CA: Coarctation of the aorta. "MI": "Mitral" insufficiency. PS: Pulmonary stenosis. "MS": "Mitral" stenosis. B 3: With bulboventricular inversion. B 4: With sinoatrial inversion.

ROENTGENOGRAPHIC FINDINGS

As with the ECG findings, the roentgenographic findings depend partly on the presence of possibly associated defects. The anomalous position of the great vessels may cause an accentuated concavity in the left border of the heart below the aortic knob, depending on the medially situated pulmonary artery. This sign may be of diagnostic value, especially if no associated malformation is present.

CATHETERIZATION AND ANGIOCARDIOGRAPHY

Helmholz and associates,[27] in 1956, reported the first case of corrected transposition diagnosed clinically. The diagnosis was confirmed by cardiac catheterization. In corrected transposition the pulmonic orifice lies posterior and rather low, so that the anomalous route taken by the catheter in reaching the pulmonary

artery is diagnostic. However, one has to study the position in both the frontal and lateral views. Also, it may often be difficult to advance the catheter into the pulmonary artery and, when other cardiac malformations are present, difficult to decide its anatomic position. Two further cases diagnosed in the same way are reported. However, the diagnostic method of choice, without doubt, is angiocardiography. In 1957, Anderson, Lillehei and Lester[2] diagnosed 6 cases on the basis of angiocardiography. Angiocardiography is thus a very valuable complement to cardiac catheterization, even in this malformation, in showing anatomic conditions more exactly. A total of 36 cases has been hitherto diagnosed in vivo, 19 of them by catheterization and/or angiocardiography, the remainder by surgery.

To be able to decide the positions of the heart chambers by means of the angiocardiograms, Anderson and associates[2] and Kjellberg and associates[30] found that the best information generally is provided by exposures in the true frontal and lateral views. The following criteria for the right chamber were used: a distinctly developed infundibulum, a crista supraventricularis bulging into the lumen, and, in the sinus region, reticular trabeculation more or less clearly related to the papillary muscles. The criteria for the left ventricle were as follows: absence of an infundibulum or only a very short one, no crista supraventricularis, more longitudinal and less marked trabeculation, and a more triangular shape, with the base facing cephalad.

SURGICAL TREATMENT

Surgical intervention against a ventricular septal defect associated with corrected transposition is more difficult than in a normal condition, depending upon the anomalously passing pulmonary artery and coronary arteries. Anderson, Lillehei and Lester[2] suggested that these ventricular septal defects are relatively more accessible for closure through an atrial cardiotomy, with the surgeon working through the right atrioventricular valve. Judging from the brief reports available to us, only 3 cases have been successfully operated upon for the concomitantly present ventricular septal defect (Walker and associates[47]).

PROGNOSIS

As expected, the outlook for the patients whose cases have been reported in the literature has been rather poor, since in most cases there have been serious associated cardiac malformations. In the whole series, 43 patients are dead, with information as to age lacking in 7 of them. The length of life in the remaining 36 is variable, ranging from 9 days to 60 years, with an average of 14 years. These figures may be compared with the mean survival time in patients with complete transposition: in those with intact ventricular septum it is 6 months, and in those with ventricular septal defect it is 3 years (Abbott[1]).

If corrected transposition alone were present, one would presume that little or no disturbance of cardiac function would occur. We have recorded 6 cases of this type, which are listed in Table II (Cases 1, 3, 5, 7, 8, 16). As to anatomic type, there are 5 cases of corrected transposition with bulboventricular inversion

(B 3), and 1 case with sinoatrial inversion (B 4). Thus in all of these cases the functional right but anatomically left ventricle works under an abnormally low pressure (pulmonary circuit) and with normal stroke volume, whereas the functional left but anatomically right ventricle works under a pressure abnormally high for this chamber (systemic circuit). In all of the cases except 2, death was due to other illnesses; for example, 1 death was due to peritonitis—in a patient at age 60. However, in 2 cases, death was due to heart failure. Both of these patients had complete A-V block, and were 35 and 36 years old, respectively.

CORRECTED TRANSPOSITION ASSOCIATED WITH "MITRAL" INSUFFICIENCY

In 1927, studying pathologically a case of corrected transposition with bulboventricular inversion associated with ventricular septal defect and isthmus-stenosis of the aorta, Wurm[51] noted anomalous insertion of chordae tendineae of the left atrioventricular valve. He did not mention the diagnosis of "mitral" insufficiency.

Doerr,[13] in 1938, reported a case with bulbus inversion and aplasia of the posterior mitral cusp. This case is unique, in this connection, because the malformation assumed the appearance of a real bicuspid mitral valve. Then in 1954, Edwards[15] described 3 pathologically studied cases which were associated with "mitral" insufficiency. In 1956, Helmholz and associates,[27] on the basis of cardiac catheterization, clinically diagnosed a case as probable "mitral" insufficiency associated with corrected transposition.

Of the 13 cases recorded by us (Table III), there were defects causing shunts in 9 cases (7 of those had ventricular septal defect, and 2 had patent ductus arteriosus). The remaining 4 cases thus belong to the classification of functionally totally corrected transposition. Anatomically, 10 cases are corrected transpositions with bulboventricular inversion, and 1 with bulbus inversion, and in 2 cases the type of transposition variant is unknown.

The anatomic malformation as underlying cause, when known, for the regurgitation through the left atrioventricular orifice is anomalous chordal insertion in 5 cases; 1 of these cases had a supravalvular ring, too (Helmholz[27]), in 4 cases there were Ebstein-like malformations, and in 1 case, aplasia of the posterior cusp of a bicuspid mitral valve. Anomalous chordal insertion means that the lower muscular extremities of the chordae tendineae insert into an abnormally situated papillary muscle or directly into the wall of the left ventricle in such a way that faulty alignment of the leaflets occurs. Prevention of deflection of the leaflets beyond the closed state is not present and, thus, insufficiency occurs.

As for the sex ratio there seems to be no sex preponderance—7 females to 5 males—thus differing in that respect from rheumatic mitral insufficiency.

The mean survival time is lower, only 8 years, in comparison with the whole material, as could be expected, because of the more complex malformation in these cases.

The diagnosis of "mitral" insufficiency has been confirmed by autopsy in 10 cases, supposed by clinical and catheterization findings in 2 cases, and made

TABLE III. CASES OF CORRECTED TRANSPOSITION ASSOCIATED WITH "MI" (13 CASES)

CASE NUMBER	AUTHOR, YEAR	AGE (YR.)	SEX	ASSOCIATED DEFECTS	TYPE	DIAGNOSED BY	NOTES
1.	Wurm, 1927	3/12	M	VSD + CA	B 3	Autopsy	Anomalous insertion. Not diagnosed as "MI"
2.	Doerr, 1938	"Newborn"	?	VSD	B 1	Autopsy	Aplasia of posterior *mitral* cusp
3.	Edwards, 1954	3/12	F	VSD	B 3	Autopsy	"Ebstein" anomaly
4.	Edwards, 1954	3	F	PDA	B 3	Autopsy	Anomalous insertion
5.	Edwards, 1954	31	F	—	B 3	Autopsy	"Ebstein" anomaly
6.	Becu, 1955	3/12	F	VSD	B 3	Autopsy	"Ebstein" anomaly
7.	Helmholz, et al., 1956	17	F	—	?	Cardiac catheterization	Probable "MI"
8.	Helmholz, et al., 1956	13	M	VSD	B 3	Autopsy	Anomalous insertion + supravalvular ring
9.	Anderson, et al., 1957	16	M	—	?	Cardiac catheterization	Diagnosed as "MS"
10.	Kernen, 1958	4/12	M	VSD	B 3	Autopsy	Anomalous insertion. Angiodiagnosis C.T. + VSD
11.	Kernen, 1958	1/12	M	PDA + CA	B 3	Autopsy	Anomalous insertion
12.	Kjellberg, et al., 1959	13	F	—	B 3	Angiocardiography	Tentative diagnosis of "MI" (electrokymography)
13.	Kjellberg, et al., 1959	6/12	F	VSD	B 3	Autopsy	"Ebstein" anomaly. Diagnosed as "MS"

VSD: Ventricular septal defect. CA: Coarctation of the aorta. PDA: Patent ductus arteriosus. B 3: With bulboventricular inversion. B 1: With bulbus inversion. MI: "Mitral" insufficiency. MS: "Mitral" stenosis.

more probable by electrokymographic recordings in 1 case. These latter 3 cases belong to the group of functionally totally corrected transposition associated with "mitral" insufficiency.

CASE REPORT

The patient, a 26-year-old man (I.R. 320917; M. 364/59), was treated at the Medical Clinic in 1958 and 1959. The family history includes nothing noteworthy; his parents are healthy and not blood relatives. He has no siblings. He had been a factory worker (veneer cutting) until 1956, and since then has undertaken variable light employments. He has not been accepted for military service.

Since childhood he has suffered from breathlessness on effort, and his parents have noticed cyanosis after heavy exercise. That, however, did not prevent him from running 60 meters in

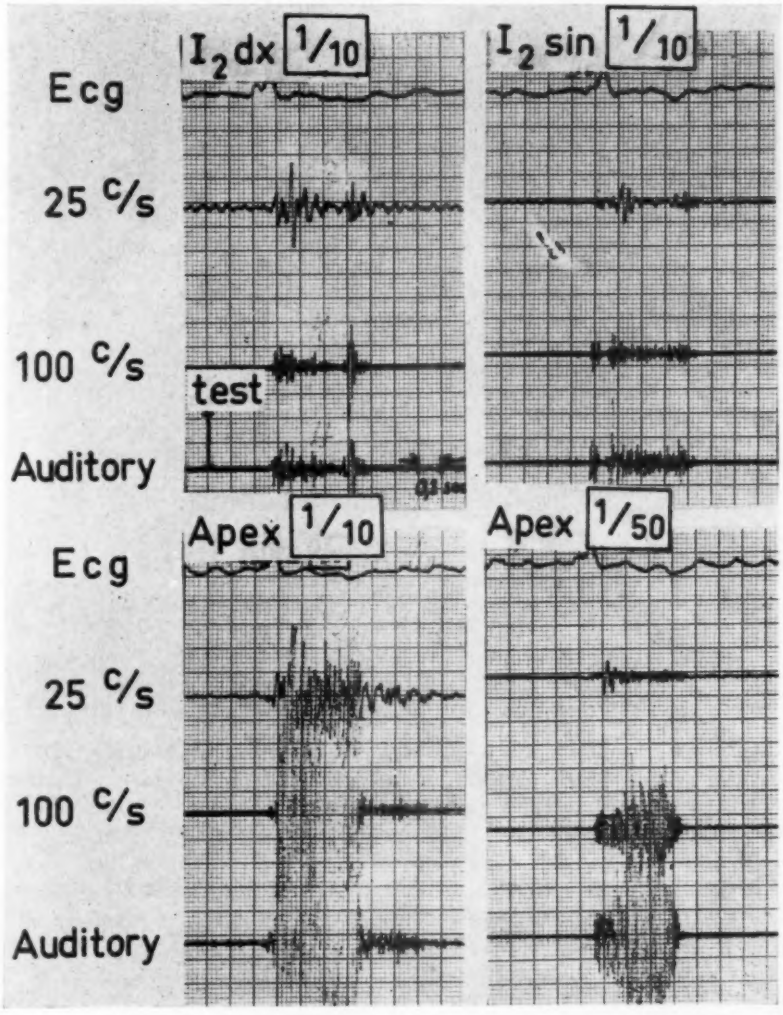


Fig. 2.—Phonocardiogram (I.R. 320917): A loud (Grade 6) systolic murmur; its maximum intensity is at the apex. A short diastolic murmur is also recorded. The second sound is split, the aortic second sound has a greater amplitude to the right of the sternum than to the left of it. Boxed figures denote the degree of amplification; the other figures denote the nominal frequencies of filters. *I_2 dx* (second right intercostal space), *I_2 sin* (second left intercostal space).

10 seconds when he was 14 years old. During the last 2 years his heart symptoms have increased, with several periods of heart failure with peripheral edema, but not pulmonary edema, hemoptysis, or systemic embolism. During that period he has been treated with digitalis and mercurial diuretics or chlorothiazide.

Physical examination on admission revealed him to be somewhat short in stature (height 166 cm.), weighing 58.8 kilograms, with labial cyanosis, some dyspnea at rest, and enlargement of the liver, which was palpable 3 fingerbreadths below the costal margins. The chest showed

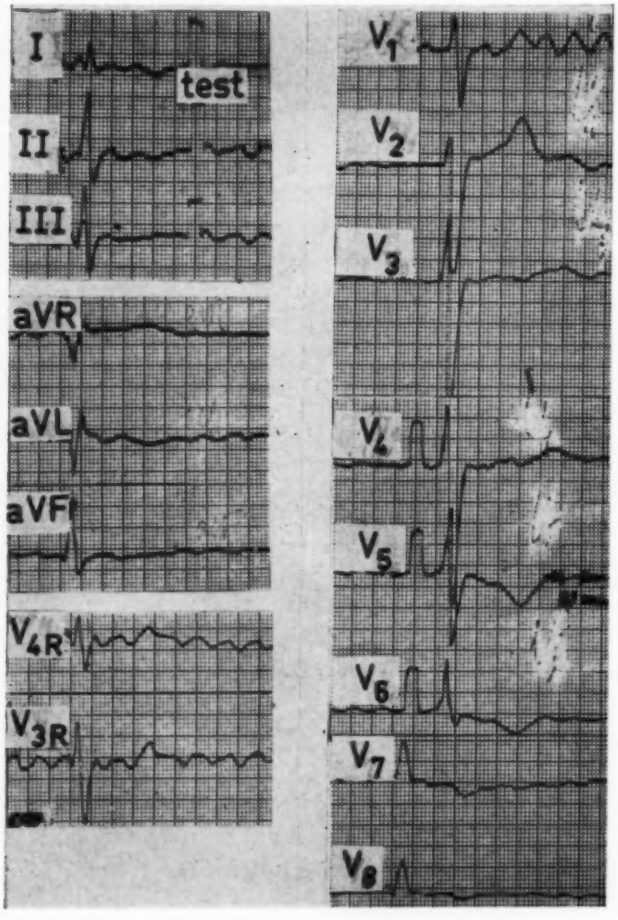


Fig. 3.—Electrocardiogram (I.R. 320917, on digitalis): Atrial fibrillation and complete A-V block. High QRS voltage. Clockwise rotation. Suspected right and left ventricular (i.e., anatomic left and right ventricular) hypertrophy. QRS complex, 0.12 sec. Positive T waves from Lead V_{4R} to Lead V_4.

a precordial bulge of moderate severity, with a steady heave over the precordial region, about the left parasternal line. The apex beat was palpated hyperdynamic in the fifth intercostal space in the anterior axillary line, where a systolic thrill was also noted. The second heart sound was accentuated in the third left intercostal space, but inaudible at the apex. There was a loud pansystolic murmur (Grade 6) with its punctum maximum at the apex, followed by a short soft diastolic murmur (see phonocardiographic recordings, Fig. 2). The heart rate was slow, 40 per minute, the rhythm regular. The blood pressure in the right and left arms was 115/80 mm. Hg; the peripheral arterial pulsations were normal.

The laboratory findings (peripheral blood counts, erythrocyte sedimentation rate, etc.) were normal, but the liver function tests revealed bilirubin in serum at a level of 2.3 to 3.8 mg. per

cent. The arm-to-tongue circulation time was 32 seconds; the venous pressure was 11 cm. of blood. Maximal breathing capacity test showed 68 liters per minute.

A 16-lead electrocardiogram showed auricular fibrillation with a complete A-V block, as judged from the complete regularity of the ventricular rate (40 beats per minute). The slow ectopic rhythm was probably of low nodal or idioventricular origin, with a widened QRS complex. Because of the ectopic impulse focus the implication of the QRS changes should, however, be regarded as uncertain (see Fig. 3).

Roentgenologic examination of the chest revealed a very much enlarged heart, total volume of 1,760 ml. corresponding to 1,050 ml./M.^{2} of body surface area. There was enlargement of both ventricles and left atrium, with an increased vascular filling of the proximal parts of the pulmonary arteries (Fig. 4). Tomography revealed no calcifications.

Fig. 4.—Frontal view. Cardiac enlargement involving both ventricles and the left atrium. Wide pulmonary arteries, suddenly narrowing outside the hilar region.

Cardiac catheterization (Fig. 5) showed a considerable pulmonary hypertension, with a systolic pressure in the pulmonary artery of 100 mm. Hg (mean pressure, 68 mm.). No signs of left-to-right shunt could be detected (the values of oxygen saturation were: in both venae cavae, 49; right atrium, 47; right ventricle, 49; pulmonary artery, 46 per cent). The arterial oxygen saturation was normal at rest (95 per cent). The resting A-V oxygen difference was therefore increased (hemoglobin concentration of blood 15.9 Gm./100 ml.), demonstrating a hypokinetic circulation. The catheter did not show in the frontal view any atypical position when lying in the pulmonary artery.

Puncture of the left ventricle by the Brock method[7] revealed a left ventricular pressure of 125 mm. Hg systolic, 20 mm. Hg end-diastolic, and no systolic pressure gradient over the aortic valves (Fig. 5). The measurement of pressures was followed by left ventricular angiocardiography (see Fig. 6). The left ventricle showed marked enlargement and increased trabeculation, and there was a considerable quantity of residual blood. There was marked mitral insufficiency, and total filling of the enlarged left atrium was obtained when the contrast in the aorta had reached the arch. The aortic orifice with the coronary arteries was apparently normal, but situated an-

teriorly and to the left. The ascending aorta was situated to the left. No contrast medium had entered any part of the right side of the heart.

Because of the enlargement and increased trabeculation of the left ventricle, and the anomalous position of the aortic orifice and ascending aorta, selective angiocardiography from the right ventricle was carried out (Fig. 7). The right ventricle was enlarged, and showed, in comparison with the left one, very slight trabeculation. The pulmonary orifice and the pulmonary trunk were situated posteriorly and to the right. The pulmonary trunk and both pulmonary arteries were all widened. There was a sudden narrowing immediately outside the hilum. No contrast medium had entered the left side of the heart.

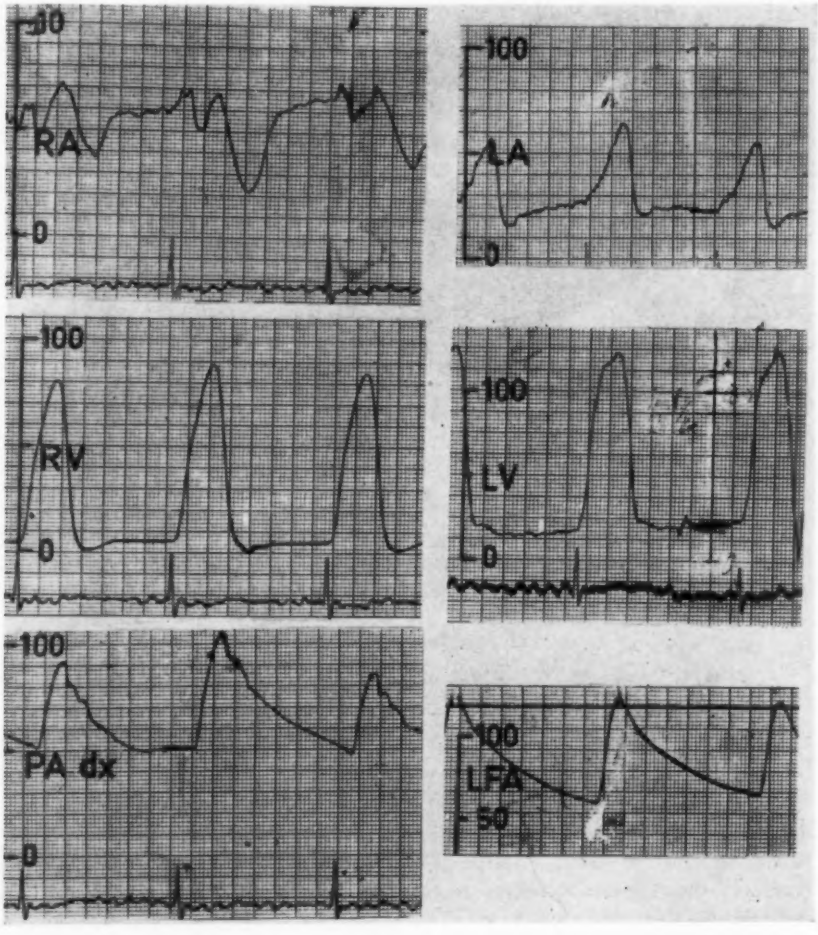
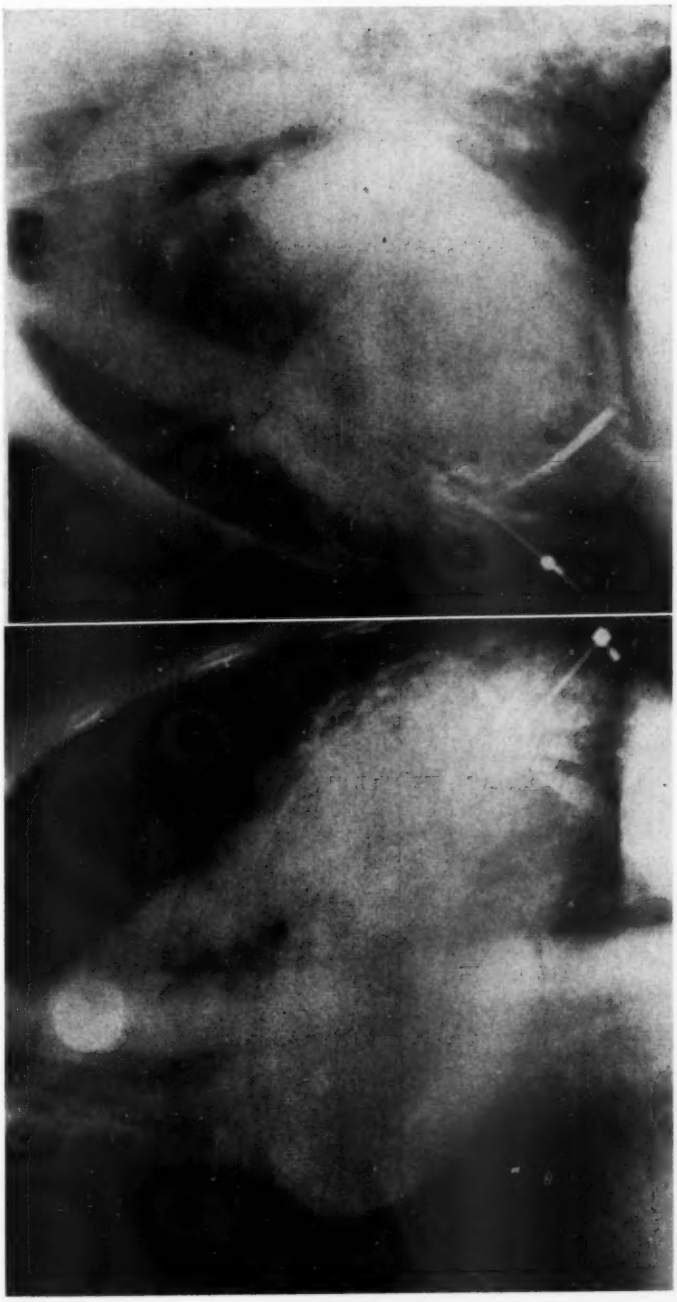


Fig. 5.—Pressure recordings (I.R. 320917). *On the left,* Cardiac catheterization: *RA* (right atrium) mean pressure, 5 mm. Hg; *RV* (functional right ventricle), 100 mm. systolic, 8 mm. Hg diastolic; *PA dx* (right pulmonary artery), 100 mm. systolic, 54 diastolic, mean pressure, 68 mm. Hg. Note the type of curve in the pulmonary artery—pulsus alternans. *On the right:* Left atrial pressure curve obtained by puncture of the left atrium: mean pressure, 34 mm. ("systolic" 61 mm.), "diastolic" 22 mm. Hg—high v-waves, atrial fibrillation. Pressure curves from *LV* (functional left ventricle): 125 systolic and 20 mm. Hg end-diastolic; *LFA* (left femoral artery): 121 systolic, 59 diastolic, 82 mm. Hg mean pressure.

Puncture of the left atrium was carried out by the Björk technique[4,6] in order to obtain more information about the mitral orifice. The following pressures were recorded: systolic, 61; diastolic, 22; and mean pressure, 34 mm. Hg (Fig. 5). Angiocardiography carried out after injection of contrast medium into the left atrium (Fig. 8) revealed rapid emptying of the enlarged atrium



B.

A.

Fig. 6.—Angiocardiograms after puncture of the left ventricle. *A*, Frontal projection, and *B*, lateral projection. Enlarged left ventricle, with increased trabeculation. Marked mitral insufficiency, with filling of the enlarged left atrium. The aortic orifice is situated more anteriorly and to the left than usual. The ascending aorta is situated to the extreme left of the root of the great vessels. No contrast medium has entered the right side of the heart. Corrected transposition.

A. *B.*

Fig. 7.—Angiocardiograms after injection of contrast medium into the right ventricle. *A*, Frontal projection, and *B*, lateral projection. The right ventricle is enlarged, with very slight trabeculation. The pulmonary orifice and pulmonary trunk lie more dorsally and to the right than normally. The pulmonary trunk and its terminal divisions are widened, but the vessels show sudden narrowing immediately outside the hilar region. There is little reflux of contrast medium through the tricuspid orifice. No contrast medium has entered the left side of the heart. Corrected transposition.

into the left ventricle, the thin mitral valves opening fully. Only the bases of the valves could be seen. Contrast medium flowed backward and forward between ventricle and atrium, indicating mitral insufficiency. There was no sign of contrast medium entering the right side of the heart. Thoracic aortography showed inversion but not transposition of the coronary arteries.

DISCUSSION

This 26-year-old man, described above, with symptoms of heart disease since childhood, presented on admission a clinical picture corresponding to mitral insufficiency; possibly associated ventricular septal defect was considered as not quite excluded. No history of rheumatic fever could be obtained, nor any family history of congenital heart disease. The electrocardiographic findings were noteworthy but of uncertain significance. However, an A-V block was present.

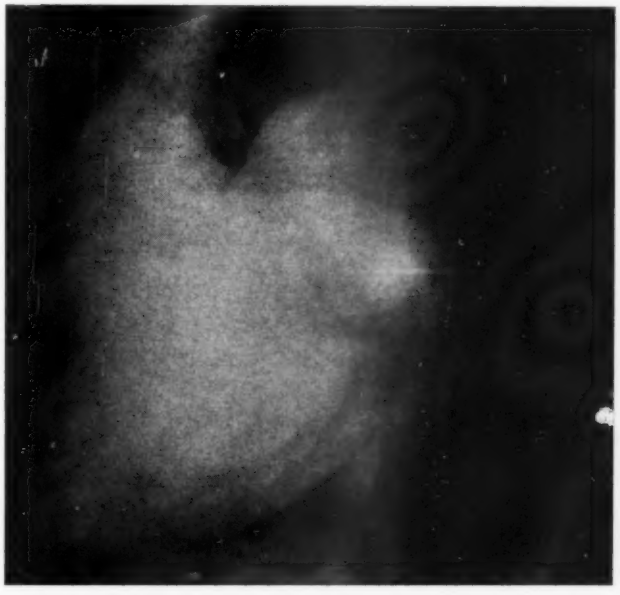


Fig. 8.—Angiocardiogram after injection of contrast medium into the left atrium. The mitral orifice is dilated. The valves are thin and fully open, and only the bases are discernible.

By cardiac catheterization a considerable pulmonary hypertension was noted, without any signs of left-to-right shunt, or right-to-left shunt at rest, the arterial oxygen saturation being normal. The catheterization did not give any further information. However, fluoroscopy during this examination was done only in the frontal view.

Angiocardiograms obtained after the injection of contrast in both the left and right ventricles revealed anomalous positions of the aorta and pulmonary artery and a situs-inversus appearance of the ventricles, without any signs of shunt. Thus, the diagnosis of functionally totally corrected transposition with bulboventricular inversion (Fig. 1, B 3) was proved.

Furthermore, a marked regurgitation through the left atrioventricular valve, in agreement with the diagnosis of its being tricuspid, was visualized by the

angiocardiogram obtained after left ventricular puncture. The "mitral" insufficiency belonged to Group III according to our classification.[5]

Puncture of the left atrium with the following angiocardiogram, together with the clinical findings, excluded a concomitant "mitral" stenosis. The left atrial pressure was considerably raised, but the diastolic pressure in the left atrium was of the same value as the end-diastolic pressure of the left ventricle. Nor could the following angiocardiogram show any signs of valvular stenosis. As to the underlying anatomic cause for the "mitral" insufficiency in this case, the negative finding of no concomitant "mitral" stenosis may indicate an anomalous chordal insertion and a secondary dilated "mitral" annulus.

Inversion but not transposition of the coronary arteries was detected. We did not find any extracardiac congenital abnormalities. The renal function, estimated by urinary findings and nonprotein nitrogen in serum, was normal. However, symptoms of liver damage, i.e., raised values of bilirubin in serum, were present. These values were interpreted as those of congestive cirrhosis.

As for surgical intervention against "mitral" insufficiency associated with corrected transposition, it may be supposed that open-heart surgery will not be performed as the annuloplasty we make in ordinary cases of mitral insufficiency. Experience from attempts to correct tricuspid insufficiency has shown that when three leaflets are present, annuloplasty alone is not sufficient. An operation with enlargement of the leaflets by plastic material has to be added, which is a more hazardous procedure than an annuloplasty.

SUMMARY

A brief review has been made of the different causes of congenital mitral insufficiency, some types of which often are associated with corrected transposition of the great vessels. Seventy-four cases of corrected transposition are recorded in the literature, 17 of which are not associated with defects causing shunt; therefore, these are termed "functionally totally corrected transposition." Furthermore, among these 74 cases are 13 cases of corrected transposition associated with "mitral" insufficiency, 4 of which are functionally totally corrected transposition. Of these 4 cases, 3 are diagnosed in vivo as probable cases. An analysis of the whole material with regard to anatomic types, sex, incidence, clinical findings, diagnostic methods, and prognostic aspects is given.

One further case of functionally totally corrected transposition associated with "mitral" insufficiency is presented. The diagnosis has been determined by cardiac catheterization and selective angiocardiographic studies with injection of contrast medium into both ventricles and left atrium. The possibilities of surgical intervention are held open; possibly, open-heart surgery may give causal treatment in a relatively near future.

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The Racial Incidence of Heart Disease at Groote Schuur Hospital, Cape Town. Part III. The Less Common Forms of Heart Disease

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In previous communications[1-3] the extremely low incidence of coronary vascular disease in the Bantu was described. In Whites, the disease is common, and in the Cape Colored the incidence lies between that of the two other races. Hypertension, on the other hand, occurs commonly in all three racial groups, but appears to be more severe in the nonwhite, particularly so in the Cape Colored female.[4] Valvular disease, especially syphilitic, is more common and more severe in the nonwhite races.

The Whites are mainly descendants of immigrants from Great Britain and the continent of Europe and are economically privileged. The Bantu occupy the lowest plane in the socioeconomic scale, providing the unskilled and heavy labor, and are descended from the people of central Africa. They are a relatively young and unstable population. The Cape Colored originate from an admixture of European, Hottentot, and Malay stock and occupy a place in the socioeconomic scale midway between the Whites and the Bantu. All three races have the same geographic and climatic environment, but the socioeconomic and genetic differences are vast.

Groote Schuur Hospital was the main hospital serving the population of Cape Town and the surrounding districts during the 5 years under review, namely, 1952-1956. It is an 854-bed hospital, with slightly more beds for white than for nonwhite patients, and serves as the main teaching hospital of the Faculty of Medicine of the University of Cape Town. During 1955 and 1956, however, the 44 teaching beds of the New Somerset Hospital, which serves the nonwhite population only, was included in this study, thus making the number of beds for white and nonwhite patients approximately equal.

It is the purpose of this study to report the incidence of the less common forms of heart disease (as obtained from electrocardiographic data) and to present the relative incidence of all forms of heart disease. Since a means test prevents

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Financial assistance for this investigation was received from the City Council of Cape Town, the Council for Scientific and Industrial Research, and the C. R. Herman Bequest Fund.

Received for publication Oct. 20, 1959.

the attendance of the wealthier section of the general population, the hospital population is selected. This scarcely affects the nonwhite patients, but results in partial exclusion of the wealthier Whites. The figures obtained in this survey are, therefore, a more accurate reflection of the Cape Colored and Bantu than of the Whites.

MATERIAL AND METHODS

The material and methods have been described in detail elsewhere.[1-3] In brief, all inpatients and outpatients attending Groote Schuur Hospital and the 44 teaching beds of the New Somerset Hospital are included in the electrocardiographic service of the Cardiac Clinic. Over 99 per cent of the 21,582 records were interpreted by the author, so that any errors in electrocardiographic interpretation were constant in all racial groups. The same physicians and surgeons see patients of all races, and equal facilities for obtaining electrocardiographic investigation are available for all groups. The majority of inpatient electrocardiograms came from the medical wards, and almost all outpatient records came from the Medical Out-Patients Department. In all cases, electrocardiograms consisted of the six limb leads and seven precordial leads, V_1-V_7.

The population distribution and breakdown has already been described (Reference 4, Table I), and, roughly speaking, the White and Cape Colored communities are equal, although there are more elderly Whites than Cape Colored. The Bantu population is artificially loaded with males between the ages of 20 and 40. The attendance of White and Cape Colored outpatients is approximately equal, and the inpatient admissions are also approximately equal (Reference 1, Table I). The Bantu subjects, although significantly fewer in number than either of the other two groups, were generally well represented in the hospital population; however, the older group was less well represented[5] (Table I). The total number of patients was 13,152, of which 7,537 were Whites, 4,795 were Cape Colored, and 820 were Bantu (Table I).

TABLE I. AGE, SEX, AND RACE DISTRIBUTION IN THE 13,152 PATIENTS

AGE	TOTAL		WHITES		CAPE COLORED		BANTU		TOTAL
	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	
0– 9	356	284	168	137	164	134	24	13	640
10–19	392	474	163	231	205	220	24	23	866
20–29	444	654	174	235	211	267	59	52	1,098
30–39	685	675	330	248	266	375	89	52	1,360
40–49	1,260	1,112	712	565	434	499	114	48	2,372
50–59	1,580	1,339	895	781	532	498	153	60	2,919
60–69	1,227	1,211	867	880	308	311	52	20	2,438
70+	827	632	651	500	153	118	23	14	1,459
Total	6,771	6,381	3,960	3,577	2,273	2,422	538	282	13,152

FINDINGS

A. *Pulmonary Heart Disease.*—Pulmonary heart disease is not a rare condition in Cape Town and its environs, judging from the number of patients referred for investigation. Although chronic bronchitis and emphysema are major contributors, many cases do not present the classic features of the disease as it occurs in highly industrialized parts of the world. Smog, air pollution, adverse weather conditions, and occupational diseases are nonexistent.

As with hypertension, the material was analyzed in two ways. In the first instance, the incidence was calculated from all cases in which the diagnosis on the request form was that of chronic cor pulmonale or chronic emphysema. Although such a diagnosis is probably not always acceptable, in that this condition is not so easy to recognize as is hypertension, coronary disease, or valvular disease, it can be accepted that no racial selection has been made in diagnosis. The second method was to subject the electrocardiograms to analysis for evidence of right ventricular or right auricular hypertrophy. In fact, particularly because the recognition of cyanosis is so difficult in the pigmented races, the diagnosis of cor pulmonale in many cases of heart failure of uncertain origin was first suggested and established on the electrocardiographic findings.

The gradings used on the basis of electrocardiographic findings were as follows: *Group 1:* The tracings appeared normal or showed positional changes with clockwise rotation only. *Group 2:* The tracings showed right auricular hypertrophy,[6] voltage change,[7] or clear evidence of right ventricular hypertrophy.[8] Incomplete and, rarely, complete right bundle branch block were included.

The interracial incidence of chronic cor pulmonale is shown in Table II. The condition is common in the three racial groups and occurred in 2.3 per cent of all cases requiring electrocardiographic investigation. No significant difference in racial incidence was found, and this has been confirmed in later studies.[9]

TABLE II. RACIAL INCIDENCE OF CHRONIC COR PULMONALE

RACE	RACIAL DISTRIBUTION OF ELECTROCARDIOGRAMS		RACIAL DISTRIBUTION OF 305 CASES OF COR PULMONALE		RACIAL DISTRIBUTION ACCORDING TO SEVERITY SHOWN IN ELECTROCARDIOGRAMS	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL	GROUP 1	GROUP 2
White	7,537	57	165	54	38	127
Colored	4,795	37	122	40	10	112
Bantu	820	6	18	6	—	18
Total	13,152		305		48	257

As in other series,[10,11] males far outnumbered females, by 4 to 1 among the Whites and Cape Colored, and by 3 to 1 in the Bantu, the peak age incidence being over the age of 50. Electrocardiographic evidence of right ventricular hypertrophy probably indicates significant pulmonary hypertension. Although there does not appear to be any direct correlation between cardiac weight, ventricular ratio, or thickness of the right ventricular wall and the electrocardiographic pattern when this shows right ventricular hypertrophy,[8] the findings of right ventricular hypertrophy compared with a normal pattern indicate a more severe involvement of the right heart.[12] On this basis, the Cape Colored tend to have a more severe involvement of the heart in chronic lung disease than do the Whites. This is probably related to socioeconomic and occupational factors.

B. *Pericarditis.*—The incidence, etiological causes, and natural history of pericarditis have been fully discussed elsewhere.[13] All cases of pericarditis diagnosed during the years 1952-1956 were subjected to special study, and a close follow-up of 160 cases was observed. Rheumatic fever, pericarditis associated with cardiac infarction, lupus erythematosus, and other collagenoses have been excluded.

The interracial incidence of pericarditis is shown in Table III. Pericarditis occurred in 1.4 per cent of all patients, males outnumbering females by 3 to 1. Whereas approximately 0.2 per cent of the Whites and 1.6 per cent of the Cape Colored had pericarditis, the incidence in the Bantu was over 10 per cent. The number of Bantu suffering from this condition is greater than that of either of the other two races, despite the overwhelmingly fewer Bantu subjects in the population at large. This has been shown to be due to the great incidence of tuberculous pericarditis in the Bantu,[13] the majority of Bantu patients (at least 70 per cent) being tuberculous. As pointed out by Phillips and Burch,[14] almost all publications concerning racial problems in tuberculosis in general indicated a greater incidence, morbidity, and mortality for tuberculosis in the "Negro" than in the White. This certainly holds for tuberculous pericarditis in the United States[15,16] and in Africa.[17-21]

TABLE III. RACIAL INCIDENCE OF PERICARDITIS

RACE	RACIAL DISTRIBUTION OF ELECTROCARDIOGRAMS		RACIAL DISTRIBUTION OF 180 CASES OF PERICARDITIS	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
White	7,537	57	19	10.5
Colored	4,795	37	78	43.5
Bantu	820	6	83	46
Total	13,152		180	

C. *Myocardial Failure of Obscure Origin and Beriberi.*—As with pericarditis, a special study with close follow-up was made in all cases of heart failure of obscure origin, including beriberi, diagnosed during the years 1952-1956. The importance of serial electrocardiograms in the diagnosis of beriberi has been re-emphasized by Schrire and Gant.[22,23] The diagnosis was thus made in 50 consecutive cases on both electrocardiographic and clinical grounds. Alcoholism was almost always present in association with malnutrition. There were 22 Cape Colored, 18 Whites, and 10 Bantu.[23] Males outnumbered females by 9 to 1. The total number of cases in which the diagnosis was suspected was 66 (Table IV).

Cardiac failure of unknown origin ("cardiopathy") is common throughout Africa.[18,24-31] The incidence of this condition is far greater in the Bantu than in other races. However, because a clear-cut disease entity has not yet been defined,

all cases of obscure myocardial failure, including myocarditis, were included in this analysis. Notwithstanding this, the incidence in the Bantu was greater that in all other races combined (Table IV).

D. *Congenital Heart Disease.*—The diagnosis of congenital heart disease is usually made on the basis of cardiac murmurs or cyanosis, and it is routine for all members of the hospital staff to request electrocardiographic study when this diagnosis is suspected. The majority of the cases (75 per cent) were referred to the author for special study in the cardiac clinic, and many were investigated by cardiac catheterization or angiocardiography. Therefore, errors in diagnosis would be the same in all three racial groups, because the same criteria of diagnosis were applied to all patients. The interracial incidence is shown in Table V. The disease is common in all three races, and totals approximately 5 per cent of all cases in which electrocardiograms were recorded. The incidence was approximately equal in males and females. There were 640 patients under the age of 10 who had electrocardiographic study, 305 being Whites, 298 Cape Colored, and 37 Bantu (Table I). Congenital heart disease accounted for 80 per cent of the cases of heart disease in this group. Congenital heart disease is said to be more common in Whites than in Negroes.[14,32] Whether the difference in incidence shown in this study has any validity is uncertain, but cognizance should be taken of the fact that the birth rate of the Cape Colored, and especially of the Bantu,

TABLE IV. RACIAL INCIDENCE OF BERIBERI AND CARDIOPATHY OF UNKNOWN ORIGIN

RACE	RACIAL DISTRIBUTION OF ELECTROCARDIOGRAMS		RACIAL DISTRIBUTION OF 66 CASES OF BERIBERI		RACIAL DISTRIBUTION OF 62 CASES OF CARDIOPATHY	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
White	7,537	57	22	33	8	13
Colored	4,795	37	25	38	20	32
Bantu	820	6	19	29	34	55
Total	13,152		66		62	

TABLE V. RACIAL INCIDENCE OF CONGENITAL HEART DISEASE

RACE	RACIAL DISTRIBUTION OF ELECTROCARDIOGRAMS		RACIAL DISTRIBUTION OF 636 CASES OF CONGENITAL HEART DISEASE	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
White	7,537	57	374	59
Colored	4,795	37	235	37
Bantu	820	6	27	4
Total	13,152		636	

far outstrips that of the Whites, and there is thus a higher proportion of nonwhite than white children under 10 years of age. On the other hand, the Whites are more likely to seek medical attention for an ailing child.

E. *Thyroid Disease.*—The diagnosis of thyroid disease was made either on the presence of nodular goiter or frank thyrotoxicosis or on myxedema. Sufficient attention was drawn to the heart for an electrocardiographic examination in 152 patients, of whom 20 had auricular fibrillation. The interracial incidence is shown in Table VI. The condition is common in the Whites, less common in the Cape Colored, and rare in the Bantu, among whom there were only 2 cases, both of which were in women. The well-known preponderance of female over male cases[33-36] was confirmed by an incidence of 4:1. Thyrotoxic heart disease may be relatively more frequent in Whites than in Negroes,[32,34,37,38] although Phillips and Burch[14] regard the incidence of thyrotoxicosis in general in the United States to be similar in the two races. Thyrotoxic heart disease has been reported rarely in the Bantu.[17,19,20]

TABLE VI. RACIAL INCIDENCE OF THYROID DISEASE

RACE	RACIAL DISTRIBUTION OF ELECTROCARDIOGRAMS		RACIAL DISTRIBUTION OF 152 CASES OF THYROID DISEASE	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
White	7,537	57	105	69
Colored	4,795	37	45	30
Bantu	820	6	2	1
Total	13,152		152	

F. *Arrhythmias.*—Paroxysmal tachycardia was found in 21 Whites, 18 Cape Colored, and 3 Bantu, whereas "lone" auricular fibrillation (auricular fibrillation unassociated with clinical coronary disease, valvular disease, hypertension, thyrotoxicosis, etc.) occurred in 153 Whites, 44 Cape Colored, and only 4 Bantu. "Lone" auricular fibrillation may well be a reflection of occult coronary vascular disease. The incidence of this disturbance in the American Negro has been described as less than that in Whites.[39-41]

G. *Miscellaneous Conditions.*—Under this heading a variety of conditions was included. Ionic equilibrium disturbances were encountered in 73 Whites, 105 Cape Colored, and 24 Bantu. Miscellaneous conditions, such as collagenosis, myopathies, hemochromatosis, scleroderma, sarcoid, diabetes, anemia, carcinoma, liver disease, etc., were found in 134 Whites, 77 Cape Colored, and 7 Bantu. Diabetes was an uncommon condition in the Bantu.[42] Of special interest was the complete absence of pulmonary embolism in the Bantu, whereas it was found in 42 Whites and 12 Cape Colored. This is in accord with the rarity of coronary vascular disease in the Bantu, because statistically the incidence of coronary disease and embolism go hand in hand.[43]

CONCLUSIONS

The interracial incidence of heart disease as assessed on routine electrocardiographic request forms varies considerably in the three racial groups in Cape Town. This is well shown in Table VII. Thus, after excluding 4,083 normal patients (2,383 Whites, 1,412 Cape Colored, and 288 Bantu), there were 9,069 patients of whom 5,154 were Whites, 3,383 Cape Colored, and 532 Bantu. Coronary vascular disease was analyzed using rigid criteria of transmural infarction as well as ischemic patterns associated with a definite clinical picture, as previously described.[1] Possible coronary disease was suspected in 408 patients; in 214 of those (154 Whites, 59 Cape Colored, and 1 Bantu) there was either a clinical suspicion of coronary vascular disease but a normal electrocardiogram or an abnormal electrocardiogram suggesting coronary vascular disease without the clinical counterpart; the remaining 194 patients (136 Whites, 56 Cape Colored, and 2 Bantu) had patterns of left or right bundle branch block without a clinical history of coronary disease. The great disproportion in incidence of this disease in the three racial groups is clearly shown.

TABLE VII. INCIDENCE OF THE VARIOUS FORMS OF HEART DISEASE IN THE RACIAL GROUPS

DISEASE	WHITES (PER CENT)	CAPE COLORED (PER CENT)	BANTU (PER CENT)
Coronary vascular disease	26	13	1
Possible coronary disease	5.5	3.5	0.5
Hypertension	46	51	35
Rheumatic heart disease	12	25	20
Syphilitic and unknown aortic valvular disease	0.5	3.5	7.5
Pulmonary heart disease	3	3.5	3
Pericarditis	0.5	2	15.5
Beriberi and cardiopathy	0.5	1.5	5
Congenital heart disease	7	7	5
Thyroid disease	2	1.5	0.2
"Lone" arrhythmias	3.5	2	1
Miscellaneous	5	5.5	6

In Whites the incidence of heart disease was as follows: coronary vascular disease occurred in at least a quarter of the patients, and almost half of all patients were hypertensive; rheumatic heart disease accounted for 12 per cent, and congenital heart disease for 7 per cent; other conditions were uncommon.

In the Cape Colored, coronary vascular disease was half as common as in the Whites, hypertension occurred with the same frequency, but rheumatic heart disease was twice as common. Syphilitic heart disease, pericarditis, and "cardiopathy" occurred significantly more frequently than in the Whites but were relatively uncommon.

In the Bantu, on the other hand, coronary vascular disease and pulmonary embolism were excessively rare; hypertension, rheumatic heart disease, pericarditis, "cardiopathy," and syphilitic heart disease being the common cardiac conditions. These data have been confirmed in further study.[9]

SUMMARY

1. A total of 21,582 electrocardiograms from 13,152 patients attending Groote Schuur Hospital in Cape Town during 1952-1956 has been analyzed in order to determine the interracial incidence of heart disease.

2. Pulmonary heart disease occurred with equal frequency in the three racial groups, but electrocardiographic evidence of severity appeared greater in the Cape Colored.

3. Pericarditis occurred out of all proportion in the Bantu, being the third most common disease in this racial group. It was far more common in the Cape Colored than in the Whites. The high incidence of tuberculous pericarditis was mainly responsible for these findings.

4. Beriberi occurs not infrequently in all three groups, and this condition is chiefly related to the consumption of alcohol. Cardiac failure of unknown origin, "cardiopathy," is far more common in the Bantu than in other races, and accounts for a significant proportion of heart disease among the Bantu.

5. Congenital heart disease was slightly more common in the Whites and Cape Colored than in the Bantu, but the difference is probably not significant.

6. Thyroid disease requiring electrocardiographic investigation occurs more frequently in the Whites and Cape Colored than in the Bantu.

7. Auricular fibrillation without clinical evidence of coronary vascular disease, hypertensive valvular disease, or thyrotoxicosis is far more common in the Whites than in the Cape Colored, and is uncommon in the Bantu. This is presumably due to occult coronary vascular disease.

8. Pulmonary embolism requiring electrocardiographic investigation was not encountered in the Bantu in this series.

9. The findings are very similar to those found during the year 1957.

I wish to thank the staff of Groote Schuur Hospital for their cooperation throughout, and Dr. J. Burger, the Superintendent, Groote Schuur Hospital, for permission to publish these results. My thanks are also due to Mrs. C. M. Hall for her assistance with the analysis of the data.

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The Innocent Systolic Murmur in Children: A Clinical Study of Its Incidence and Characteristics

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INTRODUCTION

The improved forms of therapy now available for children with congenital and acquired heart disease make it increasingly important to differentiate between the innocent and organic murmur. For the most part, it is the internist in the community who evaluates the murmur. Not infrequently, he finds the murmur is systolic and nonorganic. He attempts to ascertain the incidence and characteristics of the functional systolic murmur in children and he finds the answer is not readily obtained.

One learns that the murmur is now described as "innocent" instead of as "functional" or "physiological," which was the former designation. The accepted definition[1] states: "Innocent murmurs are usually systolic in time, more often faint than of moderate intensity and usually blowing in quality. They are often inconstant and vary in intensity with change in posture. The commonest is a systolic murmur at the pulmonic area, which is usually best heard with the patient supine and during expiration. An apical systolic murmur is also common. Such murmurs are unaccompanied by any evidence of structural disease such as enlargement of the heart, abnormal cardiac silhouette, or abnormal electrocardiogram." This general definition is not specifically descriptive for children. The most common murmur in children is not located in the pulmonic area; it is not blowing; and furthermore, an apical systolic murmur is uncommon. The recent modification[2] of Jones' "Criteria for Guidance in Diagnosis of Rheumatic Fever" states, "an innocent murmur is systolic, occasionally harsh, is heard best along the left sternal border and usually changes with position and respiration."

REVIEW OF LITERATURE

Incidence.—There are reports[3-5] which show that 8 to 20 per cent of all children of school age have an innocent systolic murmur. In other studies,[6-9]

Received for publication Nov. 20, 1959.

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the murmur was found in 40 to 60 per cent of the children examined. Schwartzmann[7] found an incidence of 44 per cent in the resting state; the incidence was increased to 86.6 per cent after vigorous exercise. It is said[10] that heart murmurs are so frequent during childhood that even in a well child the absence of a murmur rather than its presence occasions a surprise. The variability in the reported incidence of the innocent murmur in normal children may be attributed to the different clinical groups which were employed by the respective investigators. In an attempt to obtain a more uniform group selection, the author reviewed several school surveys[7,11,12] of large numbers of normal children who were 11 to 19 years of age. This revealed an incidence of 32 to 44 per cent of innocent murmurs. The next point of interest was the incidence of innocent murmur in groups of children referred by physicians for cardiac diagnosis. In three studies,[9,15,16] the incidence was 61.3, 60.4, and 60.8 per cent, respectively; in another study[14] it was 36.0 per cent.

Graphic studies[17,18] revealed a 100 per cent incidence of the innocent systolic murmur in children. In one[17] of the studies, the murmur was heard with the ordinary stethoscope in only 5 of 105 children examined. Of special interest is the recent work of Groom.[19] Using a highly sensitive heart-sound pick-up, he found a systolic murmur in 100 per cent of 36 normal medical students. The murmur was located in the second, third, or fourth left intercostal spaces. It was variable in intensity and was not audible with the ordinary stethoscope. Similar systolic murmurs were found in most recordings of fetal heart sounds during the last trimester of gestation. He concluded that this innocent systolic murmur is universal, although usually subaudible.

Characteristics.—It is claimed[20] that there is no certain method of distinguishing the organic from the innocent murmur. In a study[21] of the first fourteen years of life, the innocent systolic murmur could not be distinguished from mitral insufficiency. An attempt[22] to analyze the characteristics of the innocent systolic murmur in 300 children did not produce a criterion for its differentiation from an organic murmur. In a clinical and graphic study of 500 children aged 4 to 17 years, exhibiting mostly pulmonic systolic murmurs, Luisada and his associates[13] considered it impossible to separate innocent murmurs from organic ones. They maintained that the innocent murmur is in reality an organic murmur caused by either a rheumatic process, a mild bacterial lesion of the valve, or an allergic valvulitis.

In contrast to the afore-mentioned, there are studies[8,11,14,15,23,24] which describe characteristics of the innocent murmur and its differentiation from the organic murmur. They conclude that the most valuable criteria for the differentiation of the innocent from the organic murmur in childhood are its acoustic quality, its point of maximal intensity, and its variability. These criteria have been found valid even in the child with a history of rheumatic fever.[15,23]

THREE INNOCENT SYSTOLIC MURMURS

Some of the uncertainty and controversy about the entire subject of the innocent systolic murmur could be dispelled if it were recognized that there are three innocent systolic murmurs. One of the earliest attempts at classification[23]

differentiated two types of innocent systolic murmurs, one in the pulmonic region and the other in the midprecordium. In addition to these two types, other reports[3,12,27] mentioned a third type. One of these[3] described a type of murmur which was present with acute infections and severe anemia, and which disappeared upon correction of these. This represents the so-called hemic murmur. The other reports[12,27] mentioned a rare type of innocent murmur located at unusual sites on the chest wall. This was probably a cardiorespiratory murmur.

Using the criteria of acoustic quality, point of maximal intensity, and variability, one can classify clinically three types of innocent systolic murmurs in childhood. They are: parasternal-precordial, pulmonic, and cardiorespiratory.

1. *Parasternal-Precordial.*—The parasternal-precordial murmur was first described by Still[25] 42 years ago. He called it a "physiological bruit." The latter was usually heard just below the level of the nipple in approximately the left parasternal line. It was found mostly in children between 2 and 6 years of age. Still described it as variable in audibility and not audible in the axilla. The murmur would disappear in months or years. Its characteristic feature was noted as a twanging sound, very much like that made by twanging a piece of string. Since Still's initial description, it has been variously described as musical, buzzing, squeaky, and rasping. Phonocardiographic tracings in children with "twanging-string" systolic murmurs[26] revealed a uniform wave pattern without overtones, in contrast to those of mitral insufficiency which revealed a highly complex and irregular pattern. Other murmurs described as snorting, scraping, and grating revealed the same pattern. This pattern is produced by the vibrations of a solid structure, such as a tuning fork, and not by the vibrations of a string. Therefore, the term "vibratory" was recommended in place of "twanging-string" to describe this innocent systolic murmur. The above-mentioned graphic pattern suggests that this murmur can be attributed[27] to the vibration caused by the impact of the fluid mass or sudden change in pressure in the course of the normal hydrodynamics of the heart.

More specifically, McKusick[30] suggests that the cause of this murmur is trigonoidation of the pulmonary cusps in systole, which results in their becoming three relatively taut flaps. It may be that these are incited to vibration. He mentions also that a pericardial origin is possible, since rubbing normal serosae has sound-producing effects.

The systolic vibratory murmur is the most common innocent murmur in childhood. It may be heard in infancy, but it becomes prominent after the child is 2 or 3 years old and is most characteristic between 3 and 7 years of age. Its incidence gradually decreases as the child grows toward adolescence. This is the murmur the child "grows out of." This murmur has been described as groaning[14] in quality and loud.[28,29] According to Rhodes,[24] characteristics of this innocent systolic murmur are as follows: (1) Its point of maximal intensity is in the third or fourth intercostal space to the left of the sternal border. Sometimes, the point of maximal intensity lies between the sternum and the apex of the heart. To include these different sites, one can designate this murmur more appropriately "parasternal-precordial." (2) The intensity varies between Grades 1 and 3, most commonly Grade 2 (range of 1 to 6), and the intensity varies with position.

(3) The pitch is medium. (4) The duration is brief, occupying the first one half or two thirds of the systole.

Infrequently, the parasternal-precordial murmur may be transmitted to the axilla. Auscultation with the patient in the left lateral position will reveal that the murmur still has its maximal intensity at the sternal margin. Because of this finding it is Rhodes' contention that innocent systolic murmurs in children with maximal intensity at the apex are so rare that they should be considered organic until proved otherwise.

In stating the difference between innocent and organic systolic murmurs, one should correct two misconceptions. It is sometimes believed that an innocent murmur disappears after exercise, and that an organic murmur becomes louder. Studies[7,16,18,24] reveal that most innocent systolic murmurs increase in intensity with exercise. The other misconception is to judge the significance of the murmurs by the intensity. Levine[31] has emphasized the importance of grading murmurs as to their intensity, the louder murmurs being attributed to organic changes. In children, a typical murmur of mitral insufficiency may be Grade 1, whereas a parasternal-precordial murmur may be Grade 3 or sometimes even Grade 4. Taussig[28] has found that "a child with a normal heart may have an extraordinarily loud functional murmur." In some thin, younger children observed[16] on a long-term follow-up, this innocent murmur can be transmitted to the infrascapular area. Laboratory studies[8] in children with a parasternal-precordial murmur failed to disclose a previous streptococcal infection.

2. *Pulmonic.*—The second most common innocent systolic murmur occurs over the base or pulmonic area. Graphic study[27] of this murmur revealed a similarity to the parasternal-precordial murmur. In contrast to the uniform pattern of the latter, the pulmonic systolic murmur had some degree of distortion. This distortion was quite different from the highly complex and irregular pattern of the murmur of mitral insufficiency. The pulmonic systolic murmur is a short, blowing murmur which varies in intensity from Grades 1 to 3, usually being Grade 2. It is transmitted parasternally and toward the apex. The second pulmonic sound is always normal. This murmur also varies in intensity with change of position and with follow-up examination. It is often accentuated by exercise. More commonly, it is found in the adolescent.

This murmur occurs in the first part of systole when the velocity of systolic ejection is maximal. It is thought[30] to be due to the rapid flow through the outflow tract of the right ventricle, which at this site is relatively superficial, and, possibly, to trigonoidation of the pulmonary cusps. Usually, the murmur is loudest when the subject is in the supine position and after exercise, since these are conditions which increase venous return and the stroke volume of the right ventricle.

The configuration of the body seems to play a significant role in the prevalence and/or cause of this innocent murmur. It is said[32] to be common in children and in flat-chested individuals, apparently because little lung tissue intervenes between the pulmonary conus and the sternum, so that a slight distortion of the vessels results. It is also heard when there is an abnormal configuration of the chest (pectus excavatum, kyphoscoliosis) and abnormal cardiac position

(dextrocardia with levoposition, mediastinal displacement). The murmur in these cases is probably due to compression of the pulmonary artery by the chest wall, with a concomitant increase in the cardiac ejection phase.

The so-called hemic murmur of severe anemic states is most consistently a short, systolic murmur in the pulmonary area. It is attributed[30] to an accelerated flow of blood in the outflow tract of the right ventricle and to reduced viscosity of the blood. It is also attributed[20] to dilatation of the ventricles and atrioventricular rings. Since the hemic murmur reflects an abnormal state, it should not be regarded as innocent.

There have been conflicting reports concerning the relative frequency of this murmur as compared to that of the parasternal-precordial murmur. Several reports[3,7,11,14] state that the pulmonic systolic murmur is more frequent, whereas others[8,12,15,24] state that the parasternal-precordial murmur is more frequent in childhood. For the most part, this difference can be explained by the failure of the investigator to report the incidence of the type of murmur in relation to the age of the individual child. In the afore-mentioned studies[3,7,14] there was no specific breakdown of the age group. However, it was shown[7] that in a large group of normal children who were between 12 and 19 years of age the most common innocent systolic murmur was the pulmonic. It was also pointed out that an innocent systolic murmur was still present at the age of 19 years, when it is expected to disappear. In another study[11] which found the pulmonic systolic murmur to be most common, the average age of a large number of school children examined was 13 years. These two studies lend support to the thesis that the most common innocent systolic murmur in the adolescent is the pulmonic. The other reports[8,12,15,24] state that the most common innocent systolic murmur in the first decade of life is the parasternal-precordial. The pulmonic and parasternal-precordial murmurs are said[27] to comprise 95 per cent of the innocent murmurs in children. In my series it was 98.6 per cent.

3. *Cardiorespiratory.*—The cardiorespiratory murmur is infrequently encountered in children. It is usually heard[1] at the apex or over the body of the heart at the margins of the lung. It is almost always systolic in time and varies in intensity during the phases of respiration. Inspiration sometimes decreases or abolishes it. Norris and Landis[32] describe this murmur as an interrupted or abnormal breath sound produced by the movement of the heart upon the surrounding lung tissue. It is not accurately synchronous with the heart, but often appears in the middle of systole, being distinctly separated from the first sound. It often begins and ends suddenly. It is sharply localized and seems close to the ear of the examiner as a high-pitched, short squeal.

Although the venous hum should not be mistaken for a systolic murmur, it may be worth while to draw attention to this innocent phenomenon, for it is a common occurrence in children. A venous hum[33] was found in 50 per cent of children under 12 years of age and in 30 per cent between 12 and 15 years of age. It is most frequently found in children between the ages of 3 and 6 years, in which group its incidence is 66 per cent. It appears to have its origin in the jugular vein at the junction of the subclavian. The venous hum is a continuous murmur with a diastolic accentuation and is heard to the right of the

TABLE I. AGE IN YEARS. 231 CARDIAC REFERRALS

	0-1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	TOTAL
Male	7	4	6	6	12	13	13	11	15	12	8	8	1	4	3	–	3	126
Female	10	3	4	7	7	16	11	9	11	3	10	4	1	1	4	1	3	105
Total	17	7	10	13	19	29	24	20	26	15	18	12	2	5	7	1	6	231

sternum as well as to the left, beneath the clavicle. Frequently, it is heard better in the supraclavicular fossa, varying between Grades 1 and 3, and is often high-pitched. It is louder when the child is in the erect position than in the supine. The pulmonic first and second sounds can be heard to have good quality above the background of the venous hum. The cardinal feature of the venous hum is its decrease in intensity or disappearance with rotation of the head or pressure over the neck veins.

TABLE II. DIAGNOSIS OF 231 PEDIATRIC PATIENTS REFERRED FOR CARDIAC EVALUATION

DIAGNOSIS		NUMBER	PER CENT
Innocent murmurs		146	63.3
No cardiac disease or murmur*		14	6.1
Probable rheumatic fever†		1	0.4
Rheumatic fever‡		11	4.7
Rheumatic heart disease		17	7.3
RHD, MI	(6)		
RHD, MS	(1)		
RHD, AI	(1)		
RHD, MI, MS	(5)		
RHD, MI, AI	(1)		
RHD, MI, AS	(1)		
RHD, MI, MS, AI	(2)		
Congenital heart disease		42	18.2
Ventricular septal defect	(17)		
Probable ventricular septal defect	(2)		
Atrial septal defect	(6)		
Subaortic stenosis	(5)		
Pure pulmonic stenosis	(3)		
Pulmonic valvular stenosis and ventricular septal defect	(1)		
Patent ductus arteriosus	(1)		
Patent ductus arteriosus and coarctation of aorta	(1)		
Pulmonary hypertension with patent ductus arteriosus	(1)		
Tetralogy of Fallot	(2)		
Ebstein's anomaly	(1)		
Dextrocardia with situs inversus	(1)		
Cyanotic, unclassified	(1)		
Congenital atrioventricular block§			

*In addition to negative history, physical examination, and laboratory data, no murmur was heard.

†There was a total of four cases of probable rheumatic fever with innocent murmurs. Three cases were listed under the latter category.

‡Eight of these had innocent murmurs. These were not listed under innocent murmurs.

§Listed under innocent murmur.

RHD: Rheumatic heart disease. MI: Mitral insufficiency. MS: Mitral stenosis. AI: Aortic insufficiency. AS: Aortic stenosis.

TABLE III. INNOCENT SYSTOLIC MURMURS IN 146 PEDIATRIC PATIENTS REFERRED FOR CARDIAC EVALUATION

TYPE	NUMBER	PER CENT
Parasternal-precordial	124	84.9
Pulmonic	20	13.7
Cardiorespiratory	2	1.4

CLINICAL STUDY

To seek further clarification of the character and incidence of innocent murmurs, the author reviewed the records of all subjects referred to a pediatric cardiac clinic, sponsored by a privately endowed community hospital. The latter serves a population of about 87,000 and examines any indigent or private patient upon referral by a physician only. At least two qualified internists and usually a qualified pediatrician examine each referral.

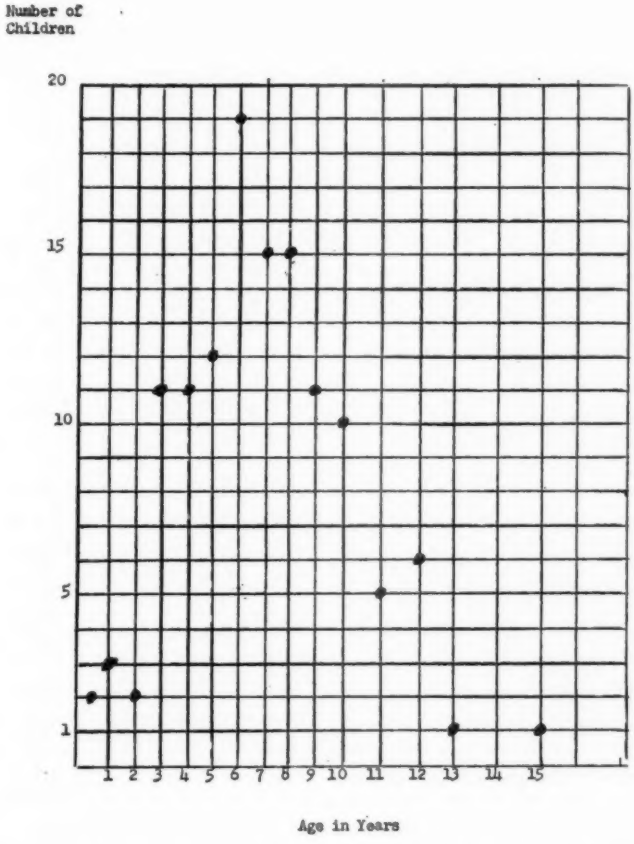

Fig. 1.—Incidence of 124 parasternal-precordial murmurs with regard to age range.

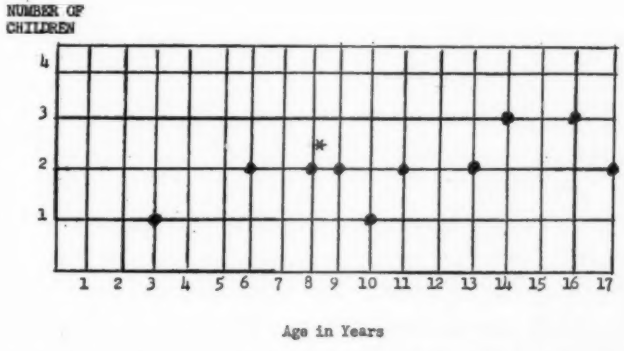

Fig. 2.—Incidence of 20 pulmonic murmurs with regard to age range. The asterisk signifies one case of moderately severe pectus excavatum.

Two hundred and thirty-one patients who were from 1 month to 17 years old have been examined. Table I shows the ages of the patients examined. They were referred because of a cardiac murmur, rheumatic fever or rheumatic heart disease, cardiac enlargement, abnormal electrocardiogram, or chest pain. Each patient was evaluated with respect to clinical history, physical examination, fluoroscopy, electrocardiogram, pertinent laboratory data, and follow-up examinations. Table II summarizes all the final diagnoses. Most of the diagnoses of organic heart disease and a few of the innocent murmurs were confirmed by the New Haven Rheumatic Fever and Cardiac Program, Yale University School of Medicine (Dr. R. Whittemore, Director). Many of the patients diagnosed as having congenital cardiac malformations underwent cardiac catheterization and/or angiocardiography. Of the 11 patients listed as having rheumatic fever, 8 had innocent murmurs. This would make an actual incidence of 66.7 per cent of innocent murmurs in all children referred for cardiac evaluation.

Table III presents an analysis of the uncomplicated innocent murmurs studied in 146 pediatric referrals. There were 124 (84.9 per cent) parasternal-precordial murmurs, 20 (13.7 per cent) pulmonic murmurs, and 2 (1.4 per cent) cardiorespiratory murmurs. In explanation of Table III it should be noted that the data were compiled from the first cardiac examination. Each patient was observed until the diagnosis was firmly established. In almost all cases, observation was made over several years. In this interim, the murmur varied between Grades 1 and 2 in intensity, occasionally Grade 3. Uniformly, all the murmurs at some time showed variability with positional change, i.e., the murmur would disappear or become considerably less intense in the erect position.

In Fig. 1 it is seen that of the 124 parasternal-precordial murmurs, 111 occurred between the ages of 0 to 10 years. This represents 61.7 per cent of all the 180 referrals in this age range. In this study, the parasternal-precordial murmur became noticeably prevalent at 3 years of age, reached its maximal frequency at 6 years of age, and persisted until 12 years of age. It was occasionally encountered before 3 and after 12 years of age.

The innocent systolic murmur over the pulmonic area was observed in 20 children; 3 cases at age 16 and 14 years; 2 cases at age 17, 13, 11, 9, 8, and 6 years, respectively; and 1 case at age 10 and 3 years, respectively. One child, age 8 years, had a moderately severe pectus excavatum (see Fig. 2). In the age group of 11 to 17 years, there were 12 pulmonic systolic murmurs. This represents an incidence of 23.5 per cent in the 51 children examined in this age range. Although the numbers in this age group are small, it suggests that the innocent pulmonic systolic murmur is second in frequency in childhood to the parasternal-precordial.

In my series there were 3 cases in which a loud (Grade 3) innocent systolic parasternal-precordial murmur was transmitted into the back. These murmurs were not accompanied by thrills. Taussig[28] states that an innocent murmur is seldom accompanied by a thrill, nor is it transmitted into the back. However, Whittemore[16] has found that a loud innocent murmur can be transmitted into the back. She thought that in this case the majority of the children were tall and thin-chested and between the ages of 7 and 10 years.

DISCUSSION

In the wake of improved forms of cardiac therapy there has been a renewed interest in the innocent systolic murmur in children. As a result, more consistent criteria for its incidence and characteristics have been obtained. The innocent systolic murmur in children is the most prevalent cardiac sign. In my series of 231 children less than 18 years of age, 146 (63.3 per cent) had uncomplicated innocent systolic murmurs. Eight children with a history of rheumatic fever also had an innocent systolic murmur, which would make the murmur's total incidence 66.7 per cent. This experience is similar to that in three other reports[9,15,16] on the examination of cardiac referrals, but differed from one other report[14] of similar referrals which found an incidence of 36 per cent. School surveys[7,11,12] of large numbers of normal children revealed an incidence of 32 to 44 per cent of innocent systolic murmurs. The entire subject of the incidence of the innocent

murmur has been challenged by phonocardiographic studies[17-19] which revealed a 100 per cent incidence of the murmur, although the murmur was frequently inaudible with the ordinary stethoscope. However, according to one study,[7] the murmur was audible with the ordinary stethoscope in 86.6 per cent of normal school children after vigorous exercise.

There are three types of innocent systolic murmurs in children. Although it is usual to recognize only two types,[7,8,11,14,23,24] three types[12,27] have been mentioned occasionally. The three types of innocent systolic murmurs are: the parasternal-precordial, the pulmonic, and the cardiorespiratory. The latter is infrequent in childhood. In my series, of the uncomplicated innocent systolic murmurs, there were 124 parasternal-precordial murmurs (84.9 per cent), 20 pulmonic murmurs (13.7 per cent), and 2 cardiorespiratory murmurs (1.4 per cent).

The relative frequency in childhood of the parasternal-precordial murmur as compared to the pulmonic has been the subject of varying statements. This can be attributed to the failure of correlating the frequency of the respective murmurs with the specific age group. It has been noted[24] that the parasternal-precordial murmur is most frequent in children, and that the pulmonic is more commonly seen in adolescents. However, no specific age-group analysis was mentioned in support of this statement and apparently none has ever been attempted. The present study reveals an incidence of 61.7 per cent of parasternal-precordial murmurs in the age group from 0 to 10 years, and an incidence of 23.5 per cent of pulmonic murmurs in the age group from 11 to 17 years.

In this study the characteristics of the respective innocent systolic murmurs were observed to be fairly well defined. (a) *Parasternal-precordial*: The parasternal-precordial murmur was vibratory in nature. At times, it had a groaning quality. Its duration was brief. Its maximal intensity was in the third or fourth left intercostal space and occasionally over the midprecordium. Rarely, it was transmitted to the axilla, but the maximal intensity was always to the right of the mid-clavicular line. The murmur varied between Grades 1 and 2 and exhibited marked variability with change of position and on follow-up examination. Rarely, it was Grade 3 and could be transmitted to the back. (b) *Pulmonic:* The pulmonic murmur was a short, blowing murmur with maximal intensity over the pulmonic region and was referred along the left sternal border toward the apex. Occasionally, it had a groaning quality. It varied from Grade 1 to 2 in intensity and occasionally was Grade 3. The murmur varied with change of position and with follow-up examination. Both the pulmonic and the parasternal-precordial murmurs were accentuated by exercise. (c) *Cardiorespiratory:* Two cardiorespiratory murmurs were observed. The murmur was a short, high-pitched squeal and was sharply located inside and below the apex. It varied with respiration.

To discharge a patient with an innocent systolic murmur from further cardiac follow-up, these criteria are used: negative clinical history; typical characteristics of an innocent systolic murmur; normal cardiac size and contour by roentgenogram and/or fluoroscopy; normal electrocardiogram.

CONCLUSION

The most common murmur in childhood is the innocent systolic murmur.

There are three types of innocent systolic murmurs: the "vibratory" parasternal-precordial, the blowing pulmonic, and the cardiorespiratory.

The "vibratory" parasternal-precordial systolic murmur is the most common in childhood. The blowing pulmonic systolic murmur is the next in frequency and tends to become more prevalent in the adolescent group as the "vibratory" parasternal-precordial murmur decreases in incidence.

In my series of 231 children referred with suspected organic heart disease, the incidence of innocent systolic murmurs was 66.7 per cent, and included 8 cases in which there was a history of rheumatic fever.

I wish to thank Dr. Allan V. N. Goodyer, Associate Professor of Medicine, Yale University School of Medicine, for his valuable criticism in the preparation of the manuscript, and Miss Adele Glogau, Cardiac Social Worker, Stamford Heart Association, for making available the necessary clinical records.

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Experimental and Laboratory Reports

Epicardial Leads in Man

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In several previous publications, we have reported the results of our investigations upon the electrical field created by the activity of the heart, as studied both on the surface[1-6] and inside the thorax, in man[7] and in the dog.[8-12] We thought that it now would be of interest to explore the epicardial surface in order to establish to what extent it is possible to correlate the surface and internal patterns with the epicardial electrograms.

The study of the activation process on the surface of the human heart has been inspired by that carried out on the dog heart. New opportunities for further study of the epicardial leads have been made available by the development of cardiac surgery. The studies devoted to this subject[13-33] have not, so far, produced entirely conclusive results. Variations in opinions and results can be attributed to several factors: (1) Only some parts of the epicardial surface have been explored. Most authors have confined their inquires to comparisons between epicardial leads and precordial leads. The posterior surface of the ventricles has not been properly explored. (2) Most recordings of epicardial electrograms have been obtained with ordinary electrocardiographs, mainly direct-writing devices of the routine clinical type. Paper speed of these records is never more than 50 mm. per second. (3) Most often the exploring electrodes, according to their size, cover a rather large portion of the epicardial surface. An electrode with a small surface was used only by Magri and Barbato. (4) Many recordings have been made from the outer layer of the pericardium, which makes the precise location of the unipolar lead uncertain.

For the foregoing reasons, we have undertaken, since 1956, new investigations in man, in a more strict manner.[34-42] Our objectives were: to produce tracings which permit exact morphologic and chronological studies, by means of adequate apparatus; to explore the epicardium as completely as possible, including the

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Received for publication Sept. 11, 1959.

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posterior surface of the ventricles; and to obtain, from a number of subjects, tracings from identical places on the epicardium, in order to compare them.

MATERIAL AND METHODS

The present report is based on the results of epicardial electrocardiography on 100 human subjects in the course of thoracic surgery. One of the subjects had a carcinoma of the lung. The others were submitted to surgery for cardiovascular disease: mitral stenosis in 86 patients, aortic coarctation in 7, persistent ductus arteriosus in 3, pulmonary valvular stenosis in 1, Fallot's tetralogy in 1, and echinococcus disease in 1.

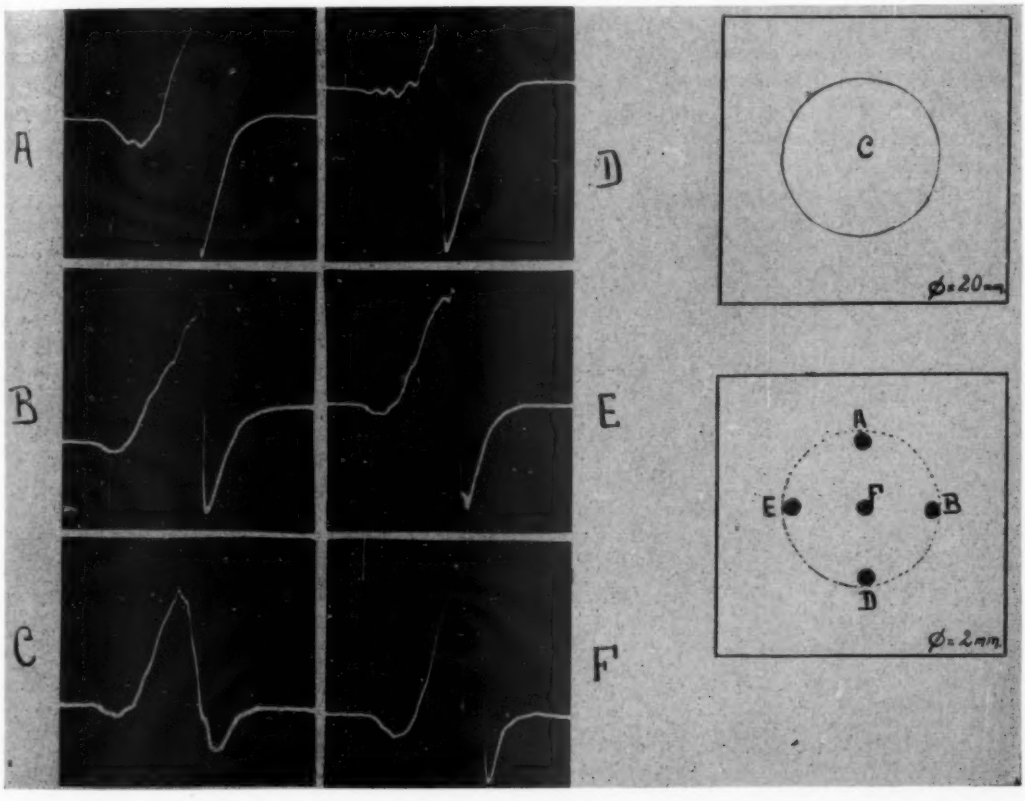

Fig. 1.—The tracing *C* was registered with an electrode 20 mm. in diameter. Tracings *A*, *B*, *D*, *E*, and *F* were registered with an electrode 2 mm. in diameter. Points *A*, *B*, *D*, *E*, and *F* were situated within the epicardial surface covered by the 20-mm. electrode. The 2-mm. electrode recorded morphologic and chronological variations between closely situated points. A good intrinsic deflection appeared on tracings *A*, *B*, *D*, *E*, and *F*. The descending limb of R in tracing *C* cannot be considered as an intrinsic deflection.

Pericardiotomy was performed only when necessary for surgical reasons (in 90 patients). Pericardial leads were so registered (in 10 patients) only when it was impossible to explore the epicardium directly.

Preoperatively, in all patients, twenty-four chest leads were registered (thoracic electric map); in 22 patients, intracavitary leads were also recorded during preoperative catheterization.

Recording Apparatus.—Except for our first ten tracings, registered with a Sanborn Poly-Viso four-channel direct-writing electrocardiograph, we used a specially designed oscillograph-camera apparatus (Cossor 1049 and Nagard DT-103 double-beam oscillograph). A capacity of 2

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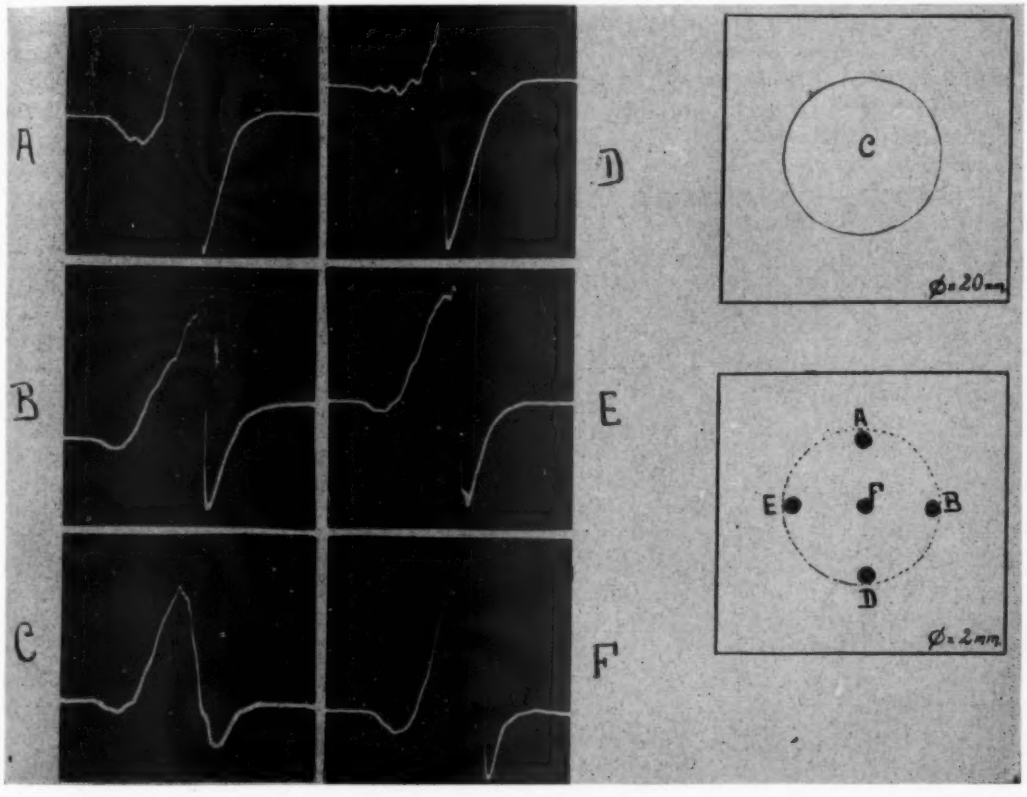

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microfarads was inserted in series in each wire of the input circuit, reducing the time constant to approximately 2 seconds, in order to avoid skin potentials; the response in frequency was constant ±5 per cent between 0.5 and 100,000 c.p.s. One of the channels traced the epicardial derivation, and the other one traced the limb lead DII, which was used as a chronological reference. The two spots moved on the same vertical axis without horizontal sweep and were photographed by a Grass C4D continuously recording camera. We chose a film speed of 100 mm. per second, which permitted a good inscription of fast accidents (mainly the intrinsic deflection) without excessive elongation of slow phenomena.

Methods of Derivation.—We used the unipolar method of derivation, the indifferent electrode being Wilson's central terminal. This method allowed us to get a good inscription of the intrinsic deflection, and to have an accurate morphologic analysis of the epicardial electrograms.

For most of our tracings, we used a metal exploring electrode smaller than 3 square millimeters. As we stated, a large surface electrode is inadequate for accurate epicardial exploration (Fig. 1). Our electrode, made of a small drop of solder, was attached to a rubber support (30 cm. long, 5 cm. wide, 0.55 cm. thick). This plate was slid between pericardium and epicardium.

Most of our tracings were recorded during mitral commissurotomy; as the patient lay in the right lateral decubitus position, the opening of the operative field provided a view centered on the left auricle. After incision of the pericardium, access was obtained to a portion of the anterior surface of the right ventricle, to a portion of the upper interventricular septum projection, and to the anterolateral portion of the left ventricle, with the exception of the apex.

The location of the electrode was governed by reference to the following anatomic structures: the anterior interventricular artery, the auriculoventricular sulcus, and the left border artery.

During the first part of the exploration, the plate was slid between pericardium and epicardium in such a way as to travel completely around the heart. Recordings were made while the operator slid it back by a continuous movement. The path followed by the plate was almost essentially the same, and a comparison between tracings from different patients was possible. In the second part of the exploration the plate was directed in various directions within the pericardial cavity (toward the apex, the right of the left border) in order to explore the whole epicardial surface (Fig. 2). Some hidden points could be explored by means of an electrode held by a rubber finger-stall on the operator's finger tip. Up to 250 epicardial derivations have been registered in the same patient; this exploration never exceeded 10 minutes.

Analysis of the Records.—Tracings were recorded on standard 35-mm. film. The pictures were enlarged to a known and constant size for examination. The order of activation of each point on the epicardium was estimated from the mid-point of the most rapid portion of the intrinsic deflection, as to a noticeable point on the limb lead DII recorded simultaneously. The times of activation were calculated from these measurements, and the origin of the time was taken as the beginning of QRS complex in Lead DII. We stated that, in most cases, the error does not generally exceed ±1.5 millisecond.

Technical considerations concerning the recording apparatus and methods of derivation were recently studied[39] and will not be discussed here.

RESULTS

In all of the patients studied a good intrinsic deflection, not exceeding 4 milliseconds, was obtained whenever the exploring electrode was in contact with the epicardial surface. With the same electrodes, nearly similar deflections were registered over the pericardial surface, but the exact location of the explored points was more difficult.

High-speed recording with high-fidelity apparatus allowed us to study with precision the aspect of epicardial complexes and to describe certain morphologic details, especially in the initial part of the ventriculogram. The first part of the rS and RS complexes was not strictly regular, and we found some notchings or slurrings on the ascendant limb of r or R. Pure rS type of complexes were rarely

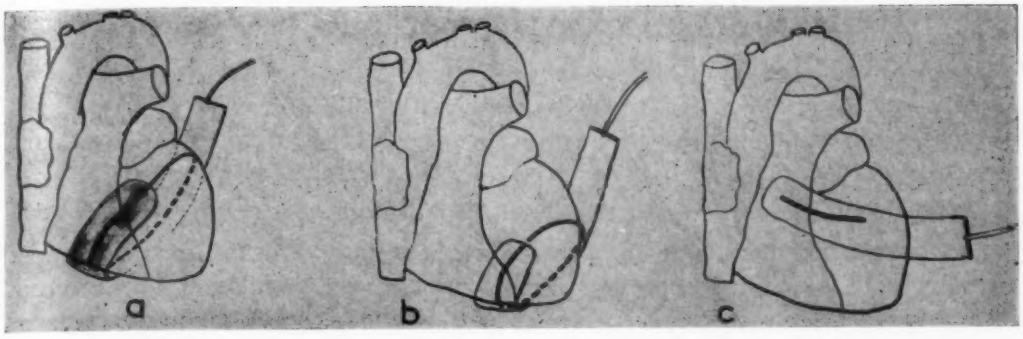

Fig. 2.—Examples of paths followed by the electrode: *a*, around the heart, upper part of the ventricles; *b*, around the heart, near the apex; *c*, from the pulmonary artery to the left ventricle across the upper part of the right ventricle.

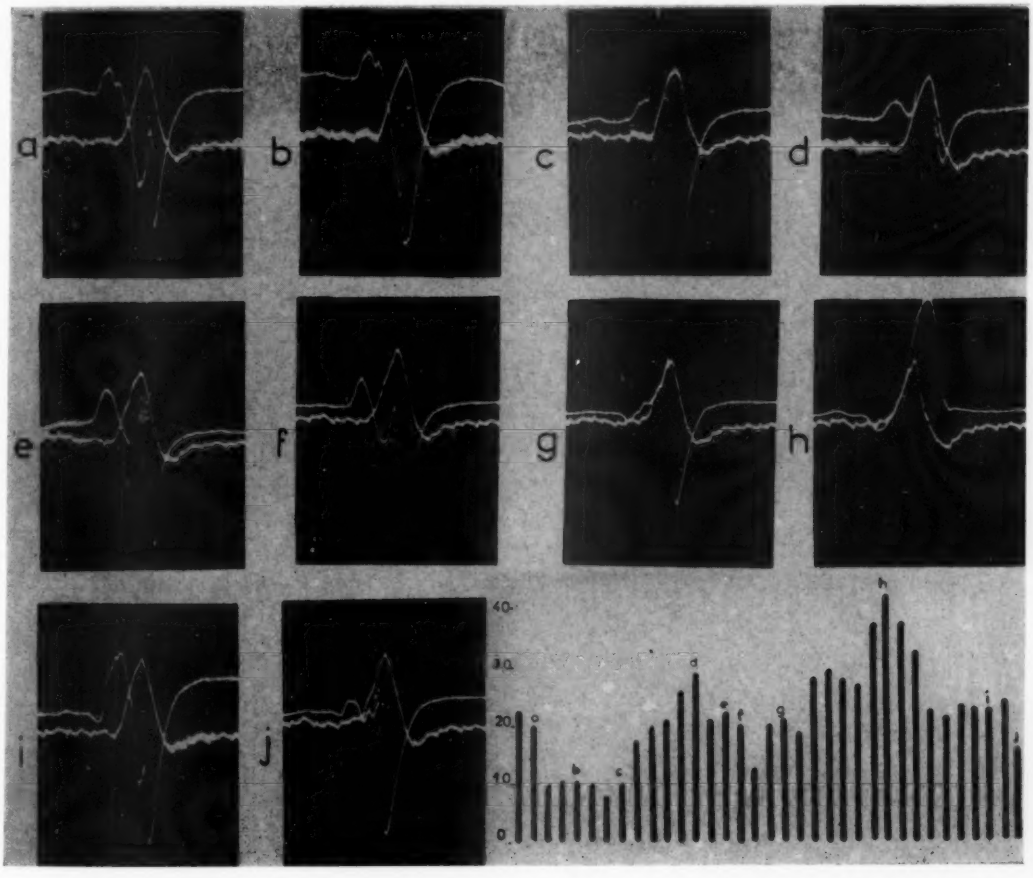

Fig. 3.—Epicardial electrograms registered all around the heart as shown in Fig. 2,*a*. Patient Ro. (with normal standard electrocardiogram). *a*, Right anterior paraseptal zone. *b*, Trabecular zone. *c*, Right ventricular free wall. *d*, Right border. *e*, Posterior aspect of right ventricle. *f*, Posterior paraseptal zone. *g*, Posterior aspect of left ventricle. *h*, Left border. *i*, Anterior aspect of left ventricle. *j*, Left anterior paraseptal zone. In the lower right-hand corner of the figure is a diagram of the times of activation expressed in milliseconds.

encountered; more often there was, before the r wave, several irregular low-voltage, positive undulations, generally of the vibrated type, and we called it "vibrated initial segment" (*segment vibré initial*) and pointed it out as (v). Further studies showed us that this (v) accident could also exist as an isolated wave, 10 milliseconds in duration, distinct from r or R wave. In the same patient the two types (vibrated segment or isolated wave) were encountered.

Epicardial Electrogram Derived From the Various Regions (*Fig. 3*).—

a. *The anterior wall of the right ventricle* is generally admitted to show almost exclusively rS or RS aspects. If rS is, in fact, most frequently encountered, numerous variations exist. Over the trabecular zone, the epicardial complexes were mainly (v)rS and sometimes rS, (v)RS, or RS (Fig. 6). *The central part of*

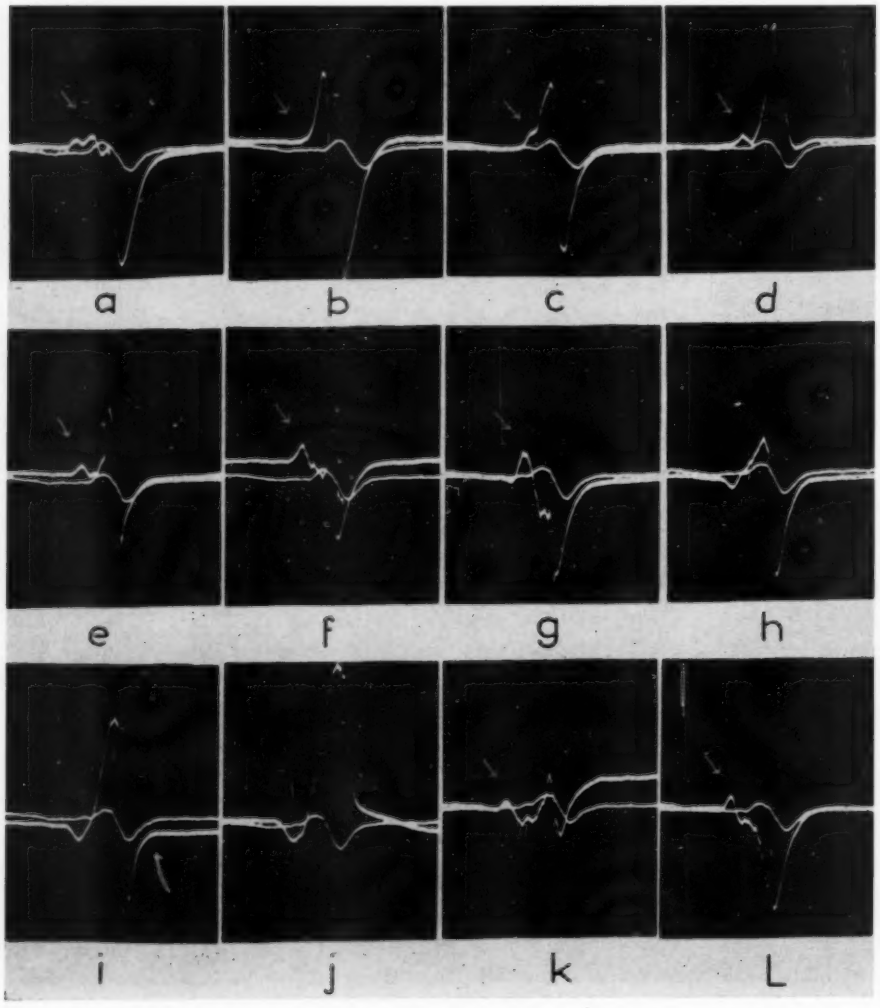

Fig. 4.—Tracings showing the various aspects of the (v) wave (indicated by the arrow). *a*, Right paraseptal zone. *b*, Trabecular zone. *c*, Right ventricular free wall. *d*, Right border. *e*, Posterior aspect of right ventricle. *f*, Right posterior paraseptal zone. *g*, Left posterior paraseptal zone. *h*, Posterior aspect of left ventricle. *i*, Posterior aspect of left ventricle. *j*, Left border. *k*, Anterior aspect of left ventricle. *l*, Left anterior paraseptal zone.

the right ventricle's anterior wall exhibited mainly (v)RS complexes, but RS, rS, or (v)rS aspects could be found on this region. In only one patient was a qRS electrogram registered (in a case of pulmonary stenosis with an important right ventricular strain) and its intrinsic deflection was delayed. *The upper part of the right anterior ventricular surface*, generally designated as "pulmonary conus," showed important variations: rS or RS complexes could be registered. We never recorded RS electrograms. On the pulmonary artery we registered polyphasic M-shaped, low-voltage complexes, without intrinsic deflection. As the electrode was moved down, the electrogram was progressively transformed into a rS or RS complex of higher amplitude. We encountered both types in patients with normal standard electrocardiogram. In cases of right ventricular strain or right bundle branch block, the Rs or R type seemed to be more frequent, and the activation time was always somewhat delayed. The edge of the right ventricle

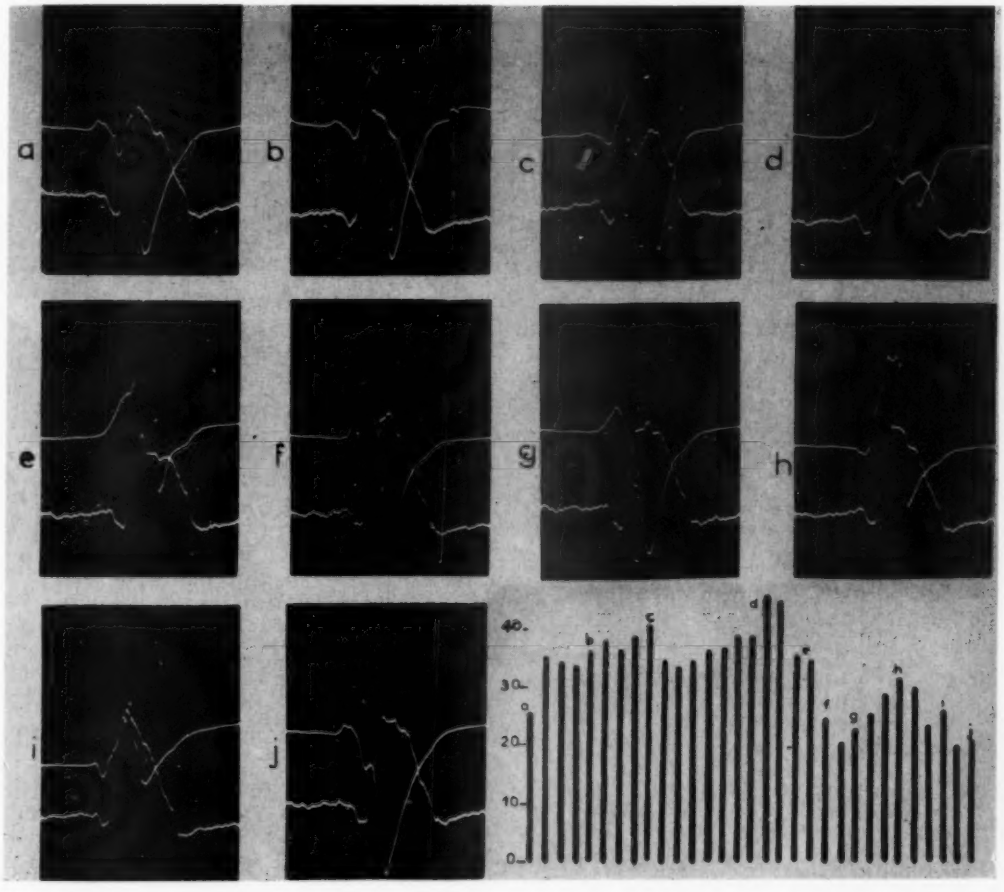

Fig. 5.—Epicardial electrograms registered all around the heart as shown in Fig. 2,*a*. Patient Ru. (standard electrocardiogram showing severe right ventricular strain). *a*, Right paraseptal zone. *b*, Trabecular zone. *c*, Right ventricular free wall. *d*, Right border. *e*, Posterior aspect of right ventricle. *f*, Right posterior paraseptal zone. *g*, Left posterior paraseptal zone. *h*, Left border. *i*, Anterior aspect of left ventricle. *j*, Left anterior paraseptal zone. In the lower right-hand corner of the figure is a diagram of the times of activation expressed in milliseconds.

yielded (v)RS or RS aspects, rS being rare. In a case of incomplete right bundle branch block, RS was found in this region, and qRS and qRs were registered in a case of severe right ventricular strain.

b. *The posterior surface of the right ventricle* showed a (v)Rs or RS aspect. But Rs, (v)rS, qRS were registered, the latter in a case of right ventricular strain.

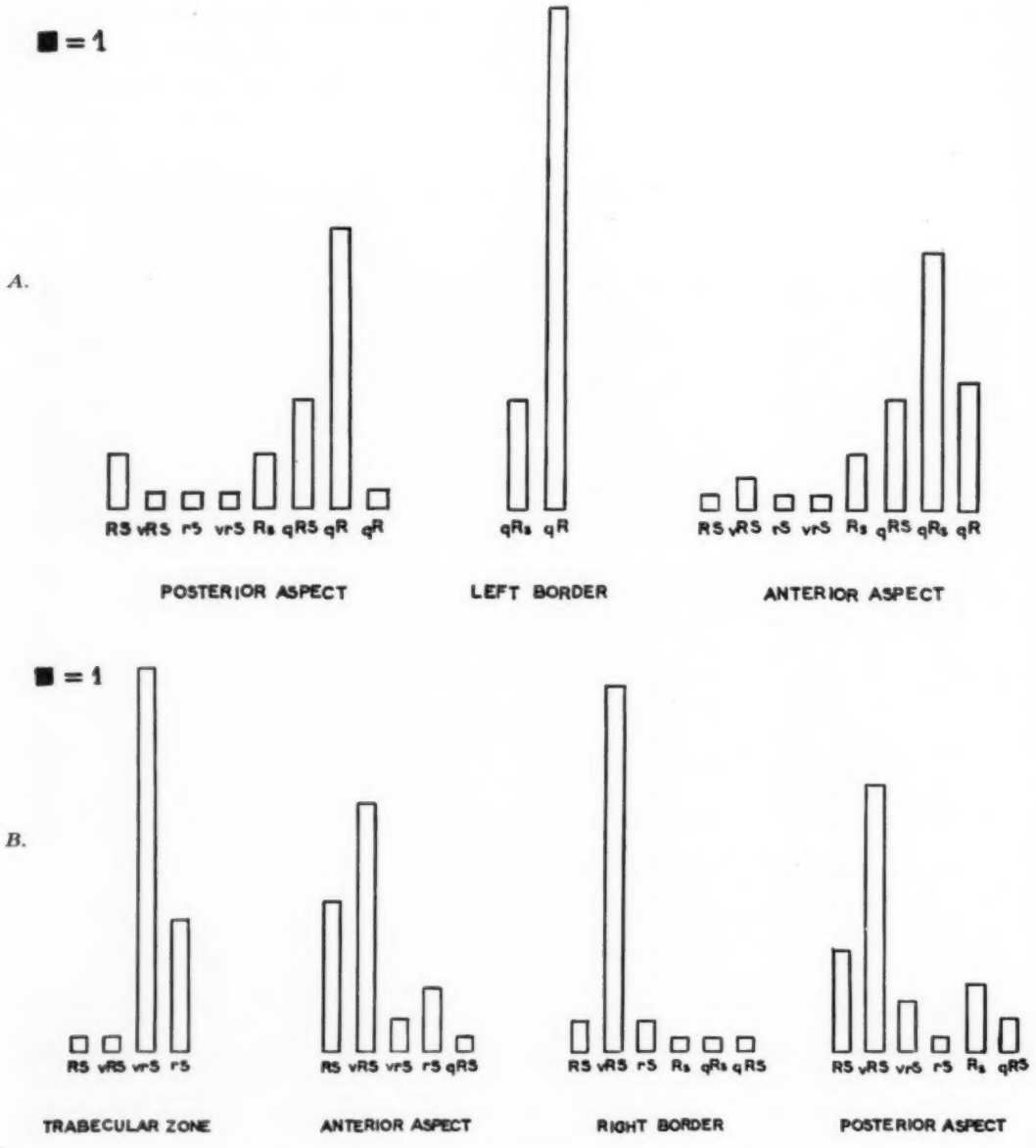

Fig. 6.—Morphologic aspect of epicardial electrograms. Diagrams based on 30 of our 100 cases in which a complete epicardial exploration was available. There is in a given area a predominant morphologic type, but somewhat different complexes can be registered in the same region. The scale is indicated by the black square (one unit). It must be noted that the sum of complexes registered in each zone often exceeds 30. This fact indicates that several electrograms showing few morphologic differences can be registered side by side in the same region. *A*, Left ventricle. *B*, Right ventricle.

c. *On the posterior surface of left ventricle,* the epicardial electrogram always yielded a tall R wave; qRS and qRs were the most frequent, but we also noticed Rs, RS, (v)RS, and (v)rS complexes.

d. *The left border* showed almost exclusively qR and qRS complexes.

e. *The anterior surface of the left ventricle* yielded qRs, qR, qRS, or RS complexes, but in the paraseptal regions, rS, (v)RS, (v)rS, and RS electrograms could be registered.

f. *The anterior and posterior projections of the interventricular septum* showed epicardial complexes of peculiar morphology. The characteristic pattern was (v)rS. The accident (v) was often registered as an isolated wave of low voltage, sometimes clearly separated from r by a short isoelectric segment. This (v) accident was more distant from r when the heart rate was slower. Its total duration time was from 10 to 25 milliseconds. It generally happened early, near about 5 milliseconds before the beginning of QRS in Lead DII. It is of particular interest to study the progressive transformation of (v) accident on both sides of the interventricular septum projection, for instance on the anterior surface of the heart.

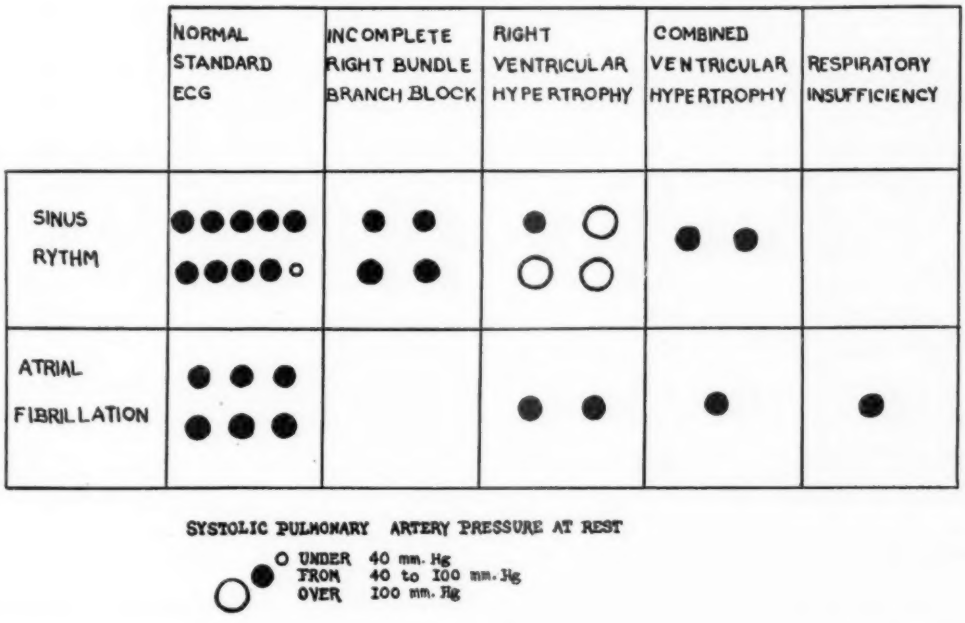

Fig. 7.

When the electrode was regularly withdrawn from the *anteroseptal region* toward the right ventricular wall, the initial (v) wave was progressively absorbed within the ascending limb of R. Sometimes it remained as an individualized accident, and the right ventricular electrograms were of the (v)RS type; in certain tracings we noticed only slurring or little notching upon the R wave.

When the electrode was regularly withdrawn toward the left ventricular wall, the early (v) wave was incorporated within the Q wave; diphasic aspects could be registered (Fig. 4).

The tracings registered on the posterior projection of the interventricular septum did not differ greatly from those recorded on the anterior projection. When the electrode was withdrawn from right to left, the morphologic transition was more rapid than on the anterior surface of the heart.

The General Process of Epicardial Activation.—There is a regular morphologic transformation and a regular chronological variation from one to another epicardial point. The depolarization wave spreads in a regular manner over the epicardium. We never found "aberrant points" as well for the timing of the intrinsic deflection as for the aspect of the electrogram.

In patients with normal standard electrocardiograms, the first region to be activated is the right ventricular free wall, namely, the trabecular zone. Next, depolarization occurs in the right and left paraseptal regions (the posterior one being depolarized a few milliseconds later than the anterior one). Then the activation wave spreads over the free walls of both ventricles and finally over right and left borders. The last region to be activated is the left border, especially in its upper portion. There is a superposition in the activation times of right and left ventricles: the later right ventricular points being activated after the earliest left points. The upper part of the right ventricular wall can be activated relatively early, or its activation can be delayed.

Right ventricular strain does not deeply alter epicardial leads. We must notice a qR aspect on the right ventricular border and neighboring areas. On the pulmonary conus, activation appears in this case to be more frequently delayed. The trabecular zone can be slightly delayed, the first electronegativity proceeding on the paraseptal zone (Fig. 5).

Incomplete or complete right bundle branch block causes a delayed activation of the right border without modifying the aspect of epicardial electrograms. The pulmonary conus frequently yields a polyphasic M-shaped complex, with a late intrinsic deflection.

Our documents concerning left ventricular strain are exclusively pericardial derivations, and cannot give precise results. Nevertheless, they indicate that left ventricular activation in these cases occurs much later than in normally activated subjects.

DISCUSSION

1. *Value of the Unipolar Method for Chronological Studies of Epicardial Activation.*—The respective values of unipolar and bipolar methods have been discussed. The bipolar method undoubtedly appears to be the best method for chronological studies. However, we used the unipolar method, although divergent opinions arose.[43-47] On the basis of good records, obtained with an adequate technique, we believe with Durrer and Van der Tweel that the most rapid portion of the intrinsic deflection (not exceeding 4 milliseconds) indicates the moment of activation of the area subjacent to the electrode. Experimental studies using synchronous unipolar and bipolar electrodes (the unipolar electrode being one of the two close bipolar electrodes) show us that the unipolar intrinsic deflection occurs at the same time as the spike of the bipolar lead. Therefore, the unipolar

method allows an accurate study of intrinsic and extrinsic waves, and a correlative study of epicardial, intracavitary, and precordial leads.

2. *Standard Electrocardiogram of Explored Patients.*—Most of our 100 patients, submitted to surgery for cardiovascular disease, presented some degree of cardiac involvement. Some of them had a standard electrocardiogram which failed to show any sign of right or left ventricular strain, or conduction abnormality. Among the 30 patients who were most completely explored, 16 had a normal standard electrocardiogram. However, we cannot assert that cardiac electrogenesis is absolutely normal in these patients.

3. From our documents we can state that there is *an approximately good concordance between the morphology of the electrograms and the time of intrinsic deflection:* the intrinsic deflection of a qR complex is always later than that of a rS complex.

4. *There is no characteristic pattern of right and left ventricles.* The qR aspect is more frequent on the left ventricle, and the right ventricle often yields rS or RS complexes. But the exploration of a great number of epicardial points brings evidence of a great morphologic diversity. The qR electrogram does not belong only to the left ventricle, but can be found also on the right border (right ventricular strain). The rS and RS patterns can be registered on both ventricles, both anteriorly and posteriorly. We cannot agree with the generally admitted opinion, according to which there is no left electrogram without a q wave, and the right electrogram is invariably of the rS type (Fig. 6).

5. *The activation of the pulmonary conus is of particular interest.* Even in normal patients, there is no characteristic patterns, rS and RS complexes being found on this region. In cases of right ventricular strain, the R wave seems to be recorded more frequently. But, as recently pointed out by Wasserburger and associates,[33] this aspect is registered only on a small portion of the pulmonary outflow tract, the neighboring regions yielding complexes of the rS type. It might be suggested that such findings are due to an incomplete exploration. However, the variability of epicardial complexes recorded on the pulmonary conus in cases of right ventricular strain has been pointed out by several authors: in 10 cases of Fallot's tetralogy, MacGregor[17] registered rS complexes in this region; Barbato[18-23] recorded also RS, Rs, rR′S, rsR′S′ in some cases of mitral stenosis and chronic pulmonary disease.

These discrepancies could be explained by the fact that the activation of the upper part of the right ventricle is essentially variable. It is well known that this region, in which the subendocardial Purkinje network is absent, is activated by the right bundle branch in 80 per cent of the cases only. Mahaim[48] showed some connections with the left bundle branch, and even with the Aschoff-Tawara node. Variations in the distribution of the excitation wave are probably more important in cases of right ventricular strain (with elective hypertrophy of the outflow tract) and in cases of high ventricular septal defect.

6. *The (v) wave,* which has not been described by previous authors, appears to be a constant component of the epicardial electrograms, especially of those registered on the anterior and posterior projections of the interventricular septum.

We suggest that this accident is the surface electrical effect of the interventricular septum. The identification of these slow potentials requires a specially designed apparatus and a registration speed of 100 mm. per second.

The epicardial electrograms registered on the paraseptal regions, both anteriorly and posteriorly, do not show pure "transition complexes," because of the mixing of the right and left parts of the electrograms. They have their own individuality.

SUMMARY AND CONCLUSIONS

1. The technique of exploration described in this paper allowed the authors (a) to record electrograms from the whole epicardial surface, including the posterior surface of the ventricles; (b) to study accurately the epicardial activation in man; (c) to describe some morphologic features of the epicardial electrogram, especially the (v) wave occurring in the first part of epicardial complexes.

2. The morphologic aspects of epicardial electrograms differ according to the zone explored. In a given area, a predominant aspect is found, but somewhat different complexes can be registered; right and left ventricles do not offer characteristic patterns.

3. In patients in whom the standard electrocardiogram fails to show any sign of ventricular preponderance or conduction abnormality, the first activated points are found on the right ventricular trabecular zone. Then anterior and posterior paraseptal zones are activated almost simultaneously. The activation wave finally reaches the right and left borders. The left border in its upper portion is the last to be activated. In case of severe right ventricular strain, the activation of the right epicardial surface is delayed. The first electronegativity is found on the anterior paraseptal zone. The right border is the last to be activated.

4. The (v) wave appears to be a constant component of the epicardial electrograms, especially of those derived from the anterior and posterior projectons of the interventricular septum. We suggest that it is the surface electrial effect of the interventricular septum.

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The Supernormal Phase of Ventricular Excitation in Man. Its Bearing on the Genesis of Ventricular Premature Systoles, and a Note on Atrioventricular Conduction

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Adrian[1] coined the term *supernormal phase* to indicate that period in the excitable cycle of the heart when electrical excitation can be produced by subthreshold stimuli. Such stimuli may be conducted with faster than normal velocity. Nahum and Hoff[2] identified the supernormal phase of ventricular excitation in the anesthetized animal as that time between the beginning of the descent of T and the inscription of U. Rigorous logical analysis[3] has been employed to suggest the presence of a supernormal phase of conduction as an explanation for rare phenomena in human arrhythmias.

The purpose of this report is to demonstrate the supernormal phase of ventricular excitation in man and to discuss its implication in the genesis of ventricular premature systoles and in the interpretation of atrioventricular conduction.

CASE REPORT

S. K., a 63-year-old man, had been completely incapacitated by almost daily, unpredictable attacks of Adams-Stokes syndrome. Because these seizures were completely intractable to medical therapy, Dr. Thomas A. Durant, Professor of Medicine, advised that the stimulating electrode of an electrical pacemaker† be securely attached to the right ventricular wall. Such an electrode, insulated by a vinyl collar except for its tip, was attached by Dr. Robert Tyson, Associate Professor of Surgery, to the right ventricular wall just lateral to the atrioventricular groove 2 cm. below the outflow tract. Before closure of the chest wall, activation of the electrical pacemaker with 7 milliamperes produced a regular ventricular rate with a pattern of left bundle branch block independent of preserved spontaneous sinus activation. Similar responses occurred immediately after operation (Fig. 1). The contour of the electrically activated premature ventricular complexes was that anticipated from premature stimulation of the right ventricle. The duration of stimulation, regardless of the current, was always constant and lasted 2.5 milliseconds.

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Received for publication Oct. 16, 1959.

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However, the following day, these premature beats changed both in contour and direction. This change could be due only to migration of the stimulating electrode, an event which was confirmed by subsequent findings. The exact location of the stimulating electrode at this time could not be determined. The direction of the premature beats was that commonly ascribed to premature activation of the left ventricle. It is possible that the stimulating electrode had migrated cephalad and close to the left main bundle because later it was at or just above the atrioventricular node.

The minimal current necessary to elicit ventricular excitation was 2.6 milliamperes. Ventricular excitation occurred only within 0.04 second after the peak of T (Fig. 2). But not every electrical pacemaker impulse of this intensity falling at this time produced electrocardiographic evidence of ventricular excitation. This experiment was repeated several times on successive days. Changing the rate of the electrical pacemaker from 40 to 120 impulses per minute did not change the time within the cardiac cycle of the appearance of electrically produced ventricular excitation. When the current was increased to 7 milliamperes, ventricular excitation continued to occur at this time. But, in addition, ventricular excitation also occurred within 0.02 second prior to the peak of T, as well as within the P-R segment (Fig. 3). This experiment was likewise repeated.

The latter ventricular complex was a fusion beat of multiform character. The closer to the origin of P it arose, the more it resembled the electrical pacemaker-induced complexes; the closer to the A-V node it arose, the more it resembled spontaneous ventricular complexes.

Further physiologic and pharmacologic studies had to be postponed because the patient developed pulmonary infarction. Ten days later, electrical excitation of the heart could not be produced by the electrical pacemaker until its current was increased to 15 milliamperes. Then, only ventricular complexes of superventricular origin were elicited (Fig. 4). Moreover, these complexes were preceded by a series of contractions of the pectoral muscle underlying the presumably indifferent electrode. These contractions were felt by the patient and seen by observers, and their electrical effects were registered on the electrocardiogram. Following a series of electrical deflections due to these muscular contractions, a premature slightly aberrant ventricular complex of supraventricular origin was elicited by the electrical pacemaker. This complex was followed immediately by normally directed, slightly aberrant atrial contraction. As the pacemaker elicited a series of ventricular complexes, the atrial contractions disappeared and then slowly emerged prior to the ventricular complexes. The P-R interval increased with each beat until the spontaneous P-R duration was reached. This series of events could be repeated provided the last pectoral contraction was not followed by a visible spontaneous ventricular contraction. This sequence of events was obtained many times on successive days.

Several days later, maximal current available from the electrical pacemaker failed to produce electrical excitation of the heart. It was obvious that the stimulating electrode was no longer in contact with the heart. This was confirmed by fluoroscopy and also by the subsequent clinical events. The patient again developed Adams-Stokes attacks. The electrical pacemaker and its attachments were detached from the patient.

DISCUSSION

Ventricular premature beats may have a constant temporal relation to the preceding dominant beat or a variable one. The former may be regarded as passive and initiated by re-entry from the sinus impulse. The latter may be regarded as active and autochthonous. If the intervals between the premature beats of the latter type are not reasonable multiples of one another, the ectopic focal stimulation is called sporadic. If the intervals are multiples, a parasystolic focus is assumed.

Such criteria are inadequate to distinguish these three types of ventricular premature beats if a supernormal phase of ventricular excitation exists in the human heart. This report suggests that such a phase is indeed present, and that it falls between the beginning of the descent of T and the inscription of U.

Fig. 1.—Ventricular premature beats of left bundle branch block type elicited by electrical pacemaker immediately after operation.

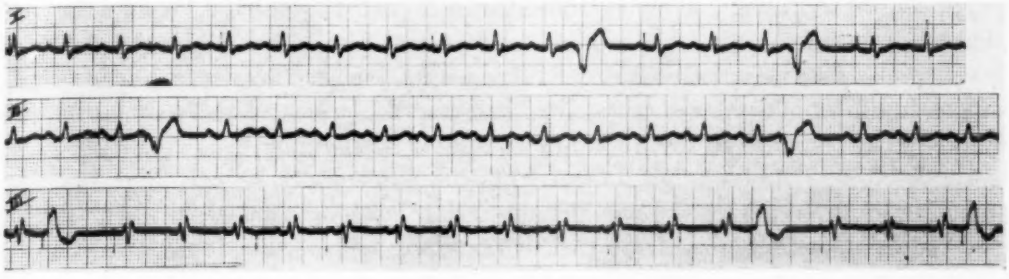

Fig. 2.—Note that the minimal current (2.6 Ma.) necessary to excite the ventricle produces an occasional ventricular premature beat at a constant time within the cardiac cycle (supernormal phase).

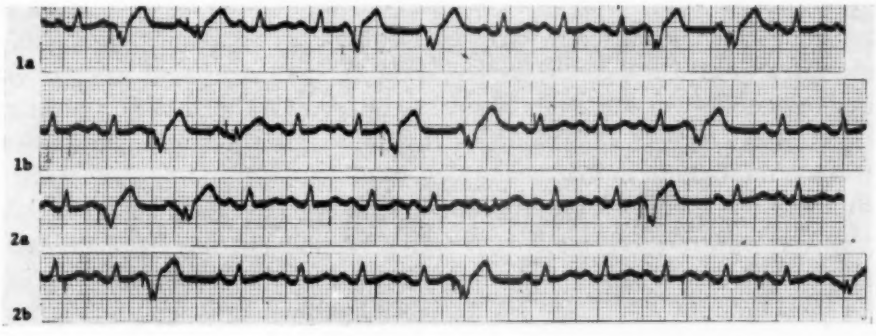

Fig. 3.—Lead II; *a* and *b* are continuous.

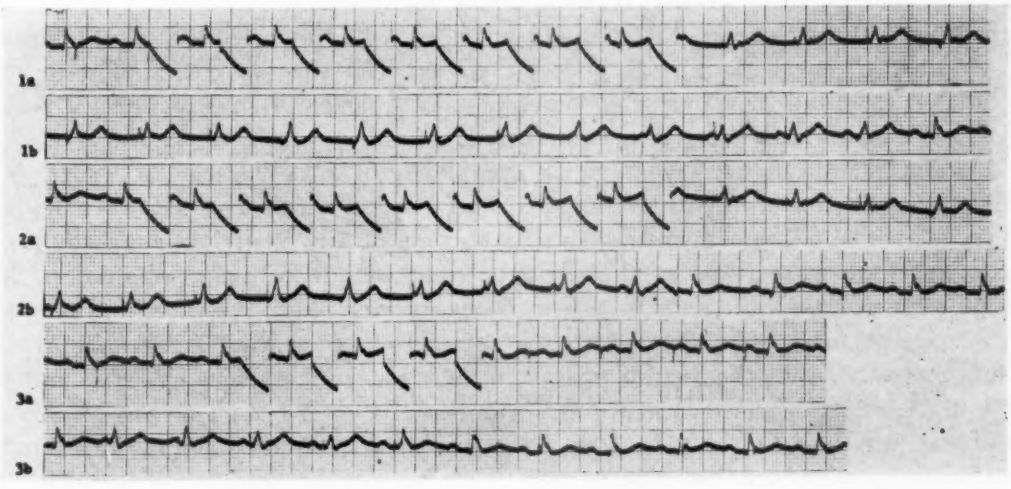

Fig. 4.—Lead II; *a* and *b* are continuous.

This time is virtually identical with that found by Nahum and Hoff in the experimental animal. Our evidence is also comparable to theirs. A subthreshold stimulus adequate for manifest ventricular excitation during the supernormal phase, regardless of its rate, must produce constant coupling. This was proved in our case by the fact that a change in the rate of the electrical pacemaker from 40 to 120 impulses per minute did not alter the time interval between a spontaneous ventricular complex and one produced by the electrical pacemaker. Furthermore, not every subthreshold stimulus occurring during the supernormal phase produced manifest electrical excitation. Similarly, Nahum and Hoff were rarely able to produce ventricular excitation in the decerebrate animal with stimuli which were successful in anesthetized ones. They attributed this difference in response to metabolic factors, and most likely to acidosis produced by anesthesia. Unfortunately, the effects of planned physiologic and pharmacologic stimuli could not be carried out in our patient because the stimulating electrode became detached from the heart. Nevertheless, this demonstration of a failure of constant supernormal excitation may make it impossible to determine the rate of a parasystolic focus. Finally, a slight change in rate of such a focus due to metabolic factors could make it impossible even to recognize the presence of parasystole. All these difficulties would be compounded by examining electrocardiographic traces of a length which is customary in clinical practice.

Several arguments have been proposed against accepting most premature ventricular systoles as being due to parasystole. One is the abolition of premature systole with sinus arrest.[4] This would be invalid for subthreshold stimuli. Another[5] is the occasional long interval between the dominant and premature beats. In such instances, one must first exclude a prolonged T-U segment. Furthermore, Mark and Langendorf's[3] concept of block when re-entry is postulated with variable coupling is equally applicable to parasystole. Constant coupling with changes in the dominant rate[4,5] is also inapplicable as an argument against the presence of parasystole of subthreshold origin. Constant coupling with identical changes in rates of the dominant and premature beats is the most cogent evidence against the presence of parasystole, unless it is possible to demonstrate that the dominant and parasystolic foci are equally affected by environmental factors.

Next to the supernormal phase, the ventricle was most excitable during the P-R interval. The fusion of ventricular complexes of supraventricular and ventricular origin are clearly recognizable.

Electrically induced ventricular complexes of superventricular origin indicated that the stimulating electrode had moved across the atrioventricular junction. The almost instantaneous excitation of the ventricle suggests that the electrode was either at the atrioventricular node or just proximal to it. The large current necessary to excite the heart was above the threshold needed to excite pectoral muscle underlying the indifferent electrode. This large current suggests either that the atrium was much more resistant to electrical stimulation than the ventricle, or, what appears more likely, that a part of the electrical current was short-circuited away from the heart. The changing impedance within the circuit was also suggested by the variation in amplitude and, rarely, in direction of the pacemaker signal. Such findings are actually explainable only

on the basis of short-circuiting of the current by the electrical pacemaker away from the electrocardiographic galvanometer.* Short-circuiting could be due to blood within the vinyl collar. If this is so, an entirely different insulation should be used in the future, if such a procedure is contemplated. The total failure of electrical excitation of the heart with the maximum current available indicated either that the stimulating electrode was no longer in contact with the heart or that most or all of the current was being short-circuited away from the heart. The latter was proved by the subsequent events.

Regardless of the cause of the large current needed to excite the atrioventricular node, no evidence of supernormal conduction could be demonstrated. Instead, the initial pacemaker-induced ventricular complex resembled in timing nodal escape. The timing phenomena of a floating P wave, synchronization, and a wandering pacemaker followed in rapid succession. These abnormalities of conduction occurring spontaneously have been difficult to explain.

The apparent wandering pacemaker is seen to be due to electrical pacemaker-induced excitation occurring progressively later in the P-R segment. Synchronization[6] can be explained by the well-known principle that when two oscillators have almost similar rates, the more susceptible or slave will temporarily assume the rate of its master. Such a mechanism has been invoked by Grant[7] to explain the mechanism of spontaneous A-V arrhythmias.

Normally directed P waves in nodal rhythm have been particularly difficult to understand. Scherf and Shookhoff[8] first claimed that such phenomena do occur.

An electrical-pacemaker stimulus subthreshold for atrioventricular excitation may provoke ventricular excitation if it is added to activity generating within the A-V node. This subthreshold stimulus may then pass retrograde to augment the ingravescent activity of the sinus node, thus firing it and producing orthograde atrial conduction. Such a mechanism could explain the phenomena of floating P waves and wandering pacemakers.

SUMMARY

Artificially produced ventricular premature beats apparently due to a supernormal phase of ventricular excitation in man is demonstrated. This phase occurs within 0.04 second of the beginning of the descent of the T wave.

Subthreshold stimuli can produce parasystole with constant coupling and may explain some hitherto obscure A-V arrhythmias.

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The Spatial Frequency Distribution of the QRS Loop as Studied on 154 Normal Individuals

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The vectorcardiogram displayed on the cathode-ray oscilloscope permits a better insight into the spatial orientation of the electrical events of the heart than does the time-based scalar electrocardiogram. The latter, on the other hand, is superior in providing direct information of the temporal sequence. A method was reported at an earlier date[1] which utilizes the advantage of the time-based scalar tracing for obtaining vectorcardiographic data. This method is employed here to study the spatial vector distribution as a function of time and to analyze the normal range of individual variation.

METHOD

One hundred and fifty-four healthy individuals, male and female in about even distribution between the ages of 20 and 50, were studied in this investigation. All individuals were screened as to their history and were examined by the investigator; special attention was paid to the cardiovascular system. All questionable or borderline cases were excluded. The individuals were classified into the groups shown in Table I.

The lead system of Helm,[2] based on data published by Frank, was employed throughout the series. The three vector leads X, Y, and Z were recorded simultaneously on film at a speed of 6 inches (152 mm.) per second (Fig. 1,*a*), and the Lissajous loops of the frontal, horizontal, and sagittal planes were displayed on the cathode-ray oscilloscope (Fig. 1,*b*). The recording instrument uses fluid-damped galvanometers in connection with an amplification system previously described[1] and has a linear frequency response from 0.1 to 2,500 cycles per second.

The scalar leads XYZ were then processed by means of a method reported at an earlier date,[1] and plane projection loops of frontal, horizontal, and sagittal planes were obtained. From these plane projections the spherical coordinates were calculated for the QRS complex. We found this method of obtaining the data from high-speed scalar tracings, as plotted with the vector coordinating instrument, to be far more reliable than oscilloscopic tracings, especially with regard to the exact determination of the tempero-spatial zero point and the initial and terminal portion of QRS.

Spherical coordinates, also called geographical coordinates, are ordinarily represented by the symbols ϕ, ψ, and r. These determine the position of a point in space: r is the distance from the origin, ϕ the geographical longitude, and ψ the colatitude. The choice of angles is arbitrary and they are frequently interchanged. Burger and Vaane[3] use longitude (ϕ) and colatitude (ψ); Schmitt and Simonson[4] use azimuth (ϕ) and elevation (complimentary angle of ψ). The reason

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Supported by grants from the Sacramento, San Joaquin, and Stanislaus County Heart Associations.
Received for publication Oct. 29, 1959.
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for using alpha (α) and tilt (T) here is the fact that the angle alpha has been used throughout electrocardiographic experience as the principal source of angular orientation for such concepts as the electrical axis, axis deviation, ventricular gradient, etc., and also for the comparison with the roentgenological angle of inclination of the longitudinal diameter of the cardiac shadow. The following simple maneuver will explain how alpha and tilt are to be understood: If we turn a world globe so that the pole axis will be directed perpendicularly toward us and thereby rotate the equatorial plane to make it parallel with the plane of Einthoven's triangle, then alpha will take the place of longitude (0° in the left axilla) and tilt that of latitude, since the pole axis will now coincide with the anatomic anterior-posterior axis (Fig. 2). A mathematical analysis of this as well as function tables of the standard geometrical system (azimuth and elevation) and the electrocardiographic system (alpha and tilt) were given previously.[5] These tables will also serve as conversion tables from one system to the other.

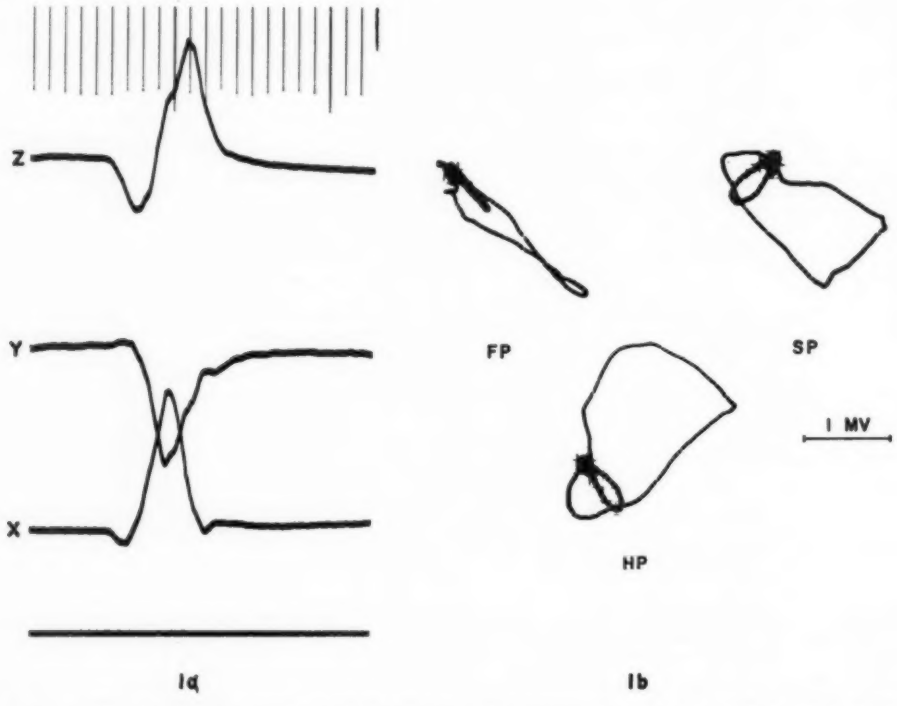

Fig. 1.—*a*, Simultaneous recording of the three scalar components X, Y, and Z. *X* = Right-left. *Y* = Head-foot. *Z* = Anterior-posterior. Paper speed, 6 inches per second. Timing lines at 0.01-second intervals. *b*, *FP* = frontal plane, *SP* = left sagittal plane, and *HP* = horizontal plane of same individual as in *a*.

The angle alpha ($\alpha°$) was read directly from the frontal plane projection. Tilt (T°) and spatial magnitude (SM) were obtained with the aid of tabulated functions.[1,5] An interpolated table was used to insure accuracy. In the region $85° < \alpha < 90°$, where the function has a steep gradient, tilt was read directly from the sagittal plane. The spherical coordinates $\alpha°$, T°, and r, thus obtained, were plotted on linear time base at 5-millisecond (msec.) intervals for all 154 individuals. These graphs served to be the element of our study. Fig. 3 shows such a graph. To understand and visualize the spherical angle frequency distribution of the groups, the values of alpha and tilt were entered into the charts seen in Figs. 4, 5, and 6. Each individual is represented by a dot at every 5 msec., indicating the angular value at the respective time interval. There are, therefore, as many dots in a vertical column as there are individuals in the group. Although the mean total duration of the normal QRS complex was found by Blackburn and Simonson[6] to be 101 msec., we did not carry our calculation of the mean angles beyond 75 msec., since the standard error will increase greatly toward the end of the QRS complex because of the decrease in the number of observations. The

mean value of alpha and tilt was calculated by resolving the instantaneous spatial vector of each individual into its direction cosines.* The mean direction, therefore, is the vector sum of unit vectors. The standard deviations of alpha and tilt represent the root mean square deviations from the mean values of alpha and tilt.

The polar vector of Burger and Vaane[3] was determined for all individuals, and its mean direction was calculated for each group in the same manner as was the instantaneous spatial vector.† The mean polar vector represents the mean principal plane of the group. Since the polar vector is the unit normal vector to the surface of the principal plane, the sum of the products of the direction cosines of the instantaneous and polar vector is equal to zero whenever the path of motion of the QRS loop lies on the principal plane.‡ A normal spatial loop may deviate from its own principal plane. Deviations from the principal plane as well as the direction angles of the instantaneous vector into this plane were calculated for Group 1F and plotted against time analogous to the angular frequency distribution of alpha and tilt. The coordinate axes of the QRS plane are determined by the maximal instantaneous vector.

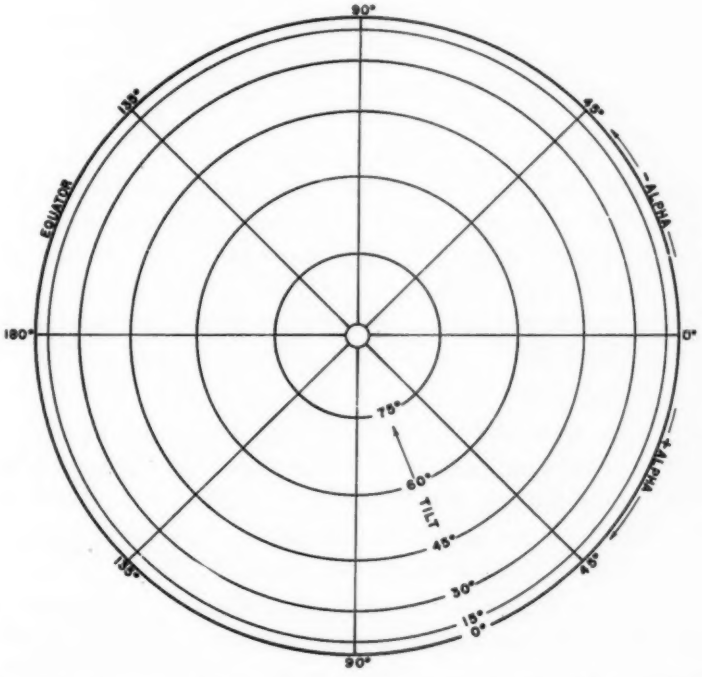

Fig. 2.—Alpha and tilt represented as longitude ($\alpha°$) and latitude (T°). The frontal plane corresponds to the equatorial plane, the pole axis to the anterior-posterior axis. $\alpha° = 0°$ in left axilla. Forward tilt carries − sign; backward tilt, + sign.

$$*\bar{\alpha}_t = \cot^{-1} \frac{\sum_{i=1}^{n} \cos A_{t,i}}{\sum_{i=1}^{n} \cos B_{t,i}}, \quad \bar{T}_t = \tan^{-1} \frac{\sum_{i=1}^{n} \cos C_{t,i}}{\sqrt{\left(\sum_{i=1}^{n} \cos A_{t,i}\right)^2 + \left(\sum_{i=1}^{n} \cos B_{t,i}\right)^2}}$$

where $\bar{\alpha}_t$ is the mean value of α at time t; $\bar{T}_t$ the mean value of T at time t; A_t, B_t, and C_t the direction angles of the spatial vector with regard to the X, Y, and Z axes at time t; i the number of individuals in the group.

†In the above-given equation, t is replaced by p; p denotes the polar vector as defined by Burger and Vaane.

‡$\cos A_t \cdot \cos A_p + \cos B_t \cdot \cos B_p + \cos C_t \cdot \cos C_p = 0$.

TABLE I

GROUP	SEX	AGE (YR.)		NUMBER
		RANGE	MEAN	
1.	F	21–30	24.8	25
2.	F	31–40	35.8	26
3.	F	41–50	45.1	26
1.	M	21–30	25.1	25
2.	M	31–40	35.6	26
3.	M	41–50	46.1	26
				154

RESULT

The Distribution of Alpha and Tilt.—The spatial vectors of a group of individuals could be represented as points on a sphere. This method was used by Brinberg[7] for the analysis of the gradient. Here we are interested in the path of motion of the QRS loop and are therefore studying the spatial angle as a function of time. The spherical angles alpha and tilt are therefore plotted against time. These are the scattergrams seen in Figs. 4-6. Their general pattern is consistent throughout the whole series.

We notice a wide scattering of alpha during the first 20 msec. in all groups. This scattering is not uniform, but shows some clustering between $-90°$ and $-180°$ except in Groups 3M. During the first 5 msec. we see no vector in the region $0° < \alpha < +60°$ in any of the six groups. As this is the region of the densest clustering during the time of maximal deflection, we must assume that the vectorhead of the first 5 msec. is not, or only exceptionally, found in the alpha region of the main deflection. It is also noticed that there is not one vector with a backward tilt during the first 15 msec. in the whole series. During this time the distribution of vectorheads shows a rather wide scattering over the four anterior octants, with the exception of the left anterior inferior octant, which is rather thinly populated during the first 10 msec. At 25 msec. most individuals have reached the main QRS direction, and as we approach 30 msec., there is a dense clustering in the region of $+10° < \alpha < +70°$. At this time we also see a gradual change of the tilt from the anterior to the posterior half. Minimal scattering of alpha is seen between 30 and 40 msec. At 45 msec. the dispersion of alpha is already increasing, and after 50 msec. the scattergram demonstrates a wide dispersion over the entire compass of alpha. The tilt is backward after 45 msec., so that we now have a scattering over the four posterior octants, with some clustering in the right posterior superior octant ($-90° < \alpha < -180°$, $0° < T < +90°$), except for Group 2M, where the clustering is more pronounced in the right

posterior inferior octant ($+90° < \alpha < +180°$, $0° < T < +90°$). The transition from anterior to posterior tilt is earlier in the female than in the male individuals, and there is more scattering between 45 and 50 msec. in Groups 3F and 3M than in the other groups. The scattergrams are given for the purpose of visualizing the pattern and range of dispersion. In areas of dense clustering, the dots merge into a solid line and their superposition prevents us from visualizing the mean values.

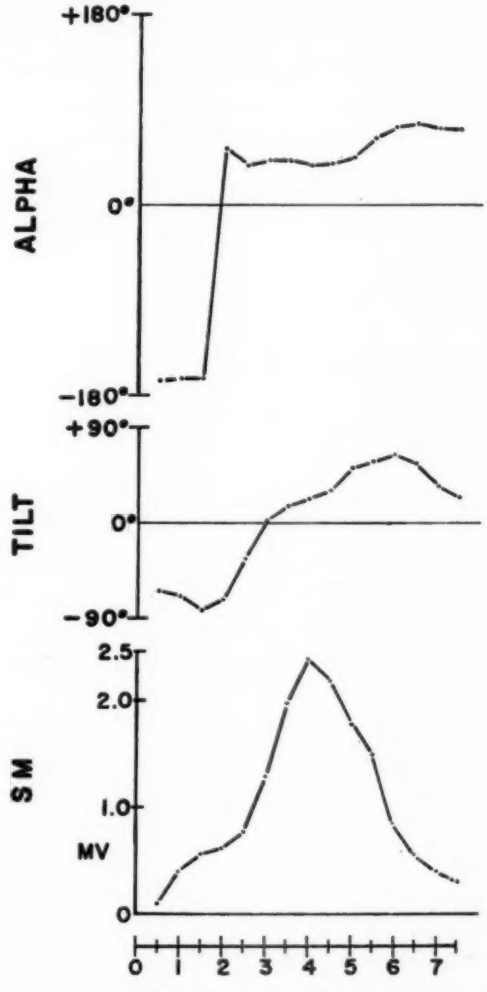

Fig. 3.—Simultaneous representation of the spherical coordinates alpha, tilt, and spatial magnitude of the QRS complex seen in Fig. 1,*a* and *b*. Linear time scale values are given as multiples of 10. 1 = 10 msec., 2 = 20 msec., etc.

Tables II and III give the mean and standard deviation values of alpha and tilt calculated in the above-described method. The reliability of the mean of the sample is related to sample size and standard deviation by the equation

$$S.E. = s\sqrt{n}$$

where S.E. is the standard error, s the standard deviation of population, and n the number of observations. It would require a larger sample to establish a true

mean value for the initial and terminal portions of the QRS complex than for the interval between 30 and 45 msec. The mean values of this time interval are, on account of their low standard deviation values, of significance for comparative studies of the age and sex groups. We see between 30 and 45 msec. (1) a decrease in alpha (counterclockwise rotation) of the corresponding instantaneous vectors with increase in age, this change being more marked in the male than in the female groups, and very much pronounced between Groups 2M and 3M; (2) alpha values in the female group slightly larger (more vertical) than the corresponding values of the male groups; (3) mean values of alpha at 35 msec. to be almost perpendicular to the mean alpha value of the polar vector in all groups.

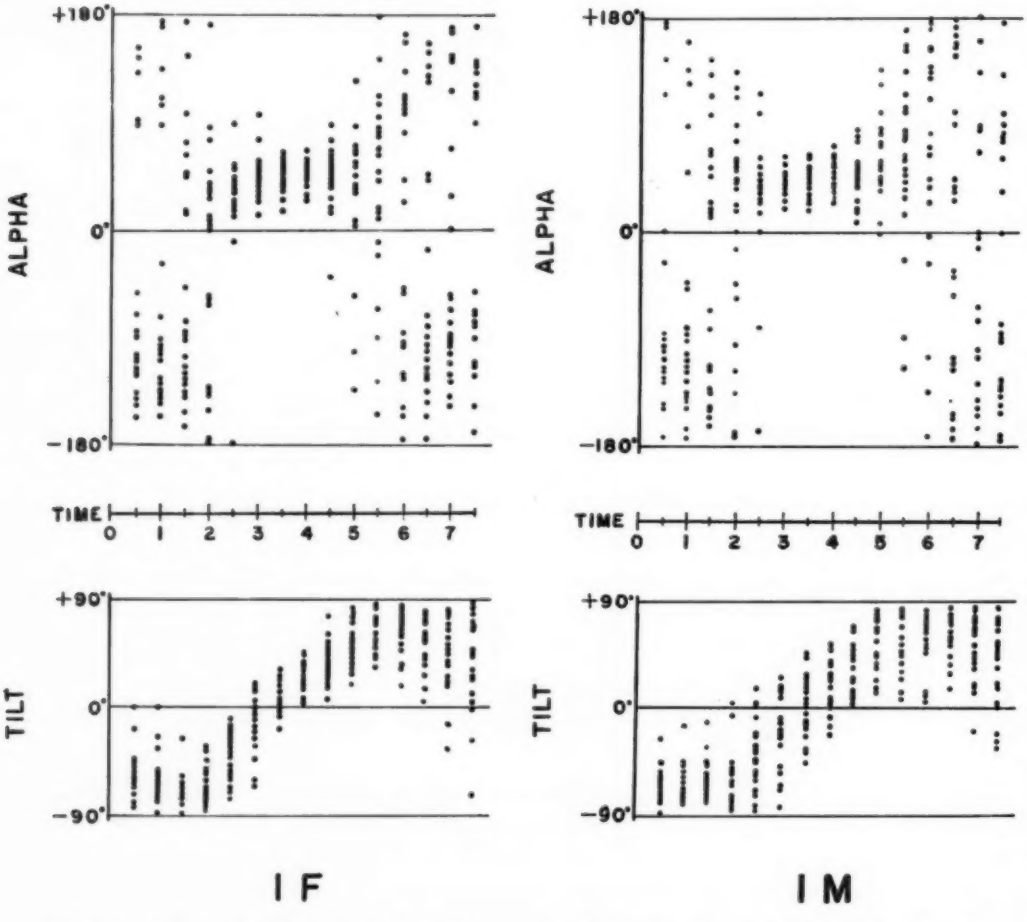

Fig. 4.—Angular distribution chart of Groups 1F and 1M. Time scale is same as in Fig. 3.

All these data refer to the narrow time range of 30 to 45 msec. The marked and irregular variations noticed in the mean alpha values of the initial and terminal portions of the group are of less significance because of the unfavorable ratio of sample size and standard deviation.

Spatial Magnitude.—Table IV contains the mean and standard deviation values of the spatial magnitudes. The standard deviation is here given in terms

of the coefficient of variation which expresses the degree of spread in percentage terms of the mean. The fact that we have no unit reference system, as the surface of the sphere in the case of the spherical angles, makes a scattergram of the spatial magnitude values less informative than those of alpha and tilt. The mean spatial magnitude curves are monotonic functions, with a peak at 40 msec. in all groups but Group 2M, in which it is seen at 45 msec. There is some skewness, showing larger vector magnitude values in the descending than in the corresponding ascending portion of the curve. The standard deviation values reach a minimum at the time of the peak and are maximal during the initial and terminal portions of the loop. We observe a decrease in the spatial magnitude values with increasing age, more pronounced in the male than in the female groups, and also

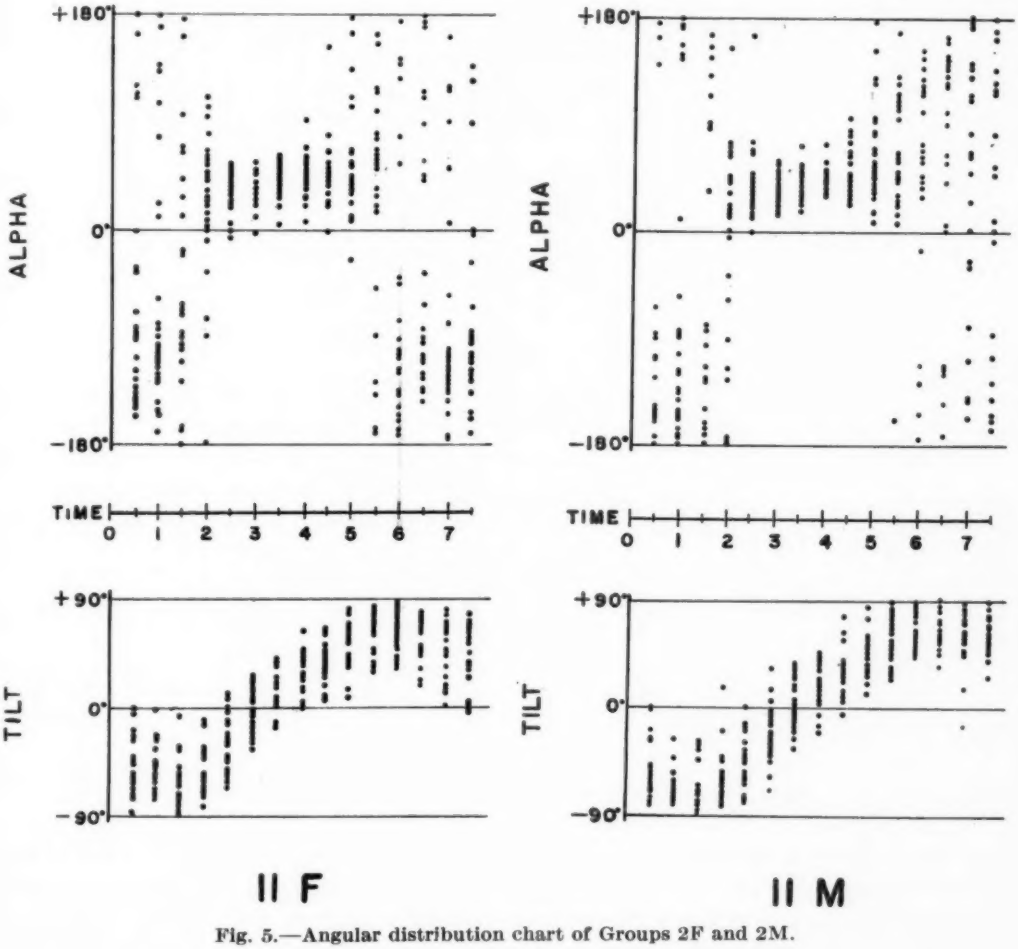

Fig. 5.—Angular distribution chart of Groups 2F and 2M.

smaller spatial magnitude values in the female groups than in the corresponding male groups. A simultaneous representation of the mean values of alpha, tilt, and spatial magnitude is given in Figs. 7 and 8.

Polar Vector.—The mean and standard deviation values of the polar vectors are given in Table V. These data represent the frequency distribution of the spatial orientation of the QRS plane. The alpha values of the polar vector show

the same pattern of change between the age and sex groups as do the alpha values of the instantaneous vectors during the time interval of 30 to 45 msec. Located in the left superior posterior octant are 74.6 per cent of the polar vectors, and the remainder are in the left superior anterior octant. A more defined spherical zone given by the values $-25° < \alpha° < -75°$, $-25° < T < +45°$ contains 93 per cent of all polar vectors if Group 3M is excluded. Only 73 per cent of the polar vectors of Group 3M are found in this zone.

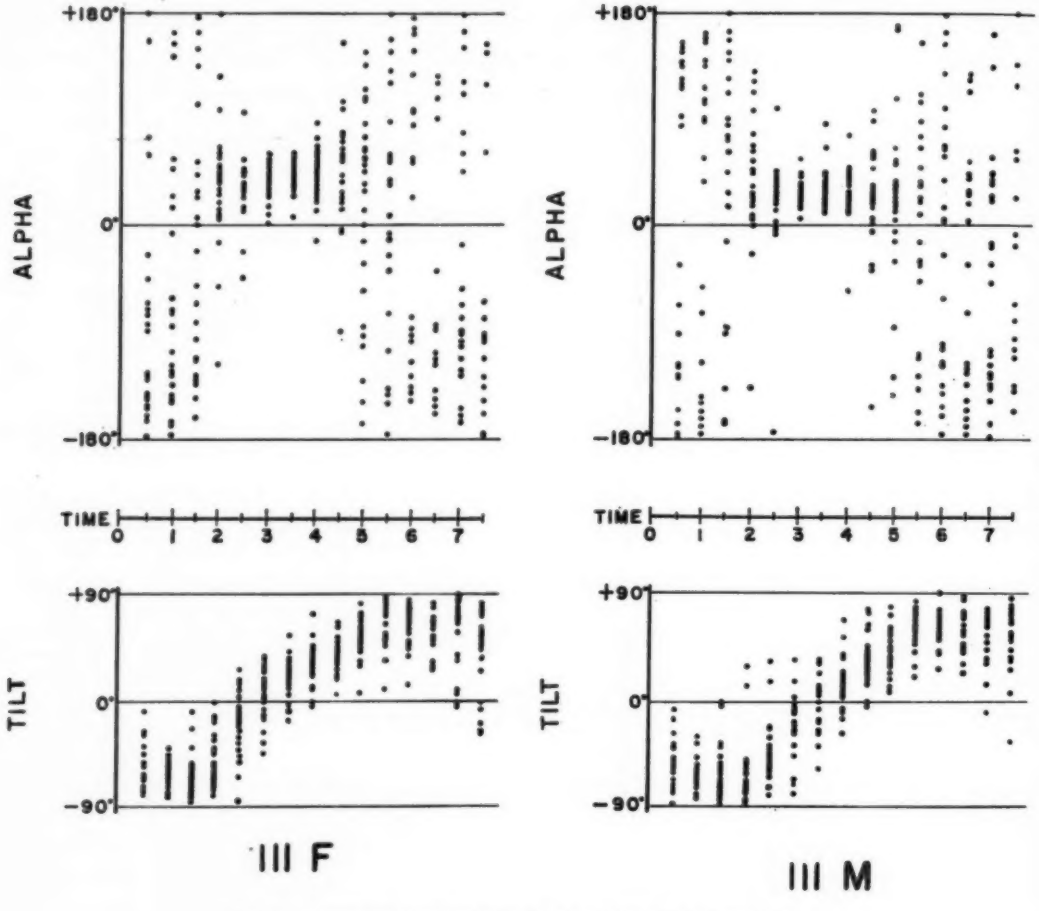

Fig. 6.—Angular distribution chart of Groups 3F and 3M.

Open Plane Projection.—A scattergram representing the distribution of the direction angle of the instantaneous vector into the open plane projection and the angle of deviation from the principal plane is seen in Fig. 9. The angle represented in Fig. 9,*A* is the same as the open plane projection vector of Milnor,[8] also viewed on the caudad surface of the QRS plane; the only difference is that the position of the plane is here given by the polar vector. The scatter seen in Fig. 9,*A* is not nearly so wide as that of alpha. It reaches the minimum at 40 msec., which is the peak value of the mean spatial magnitude curve of this group. The deviation from the plane toward the polar vector (+) and away from the polar vector (−) is rather symmetrically distributed, as seen in Fig. 9,*B*.

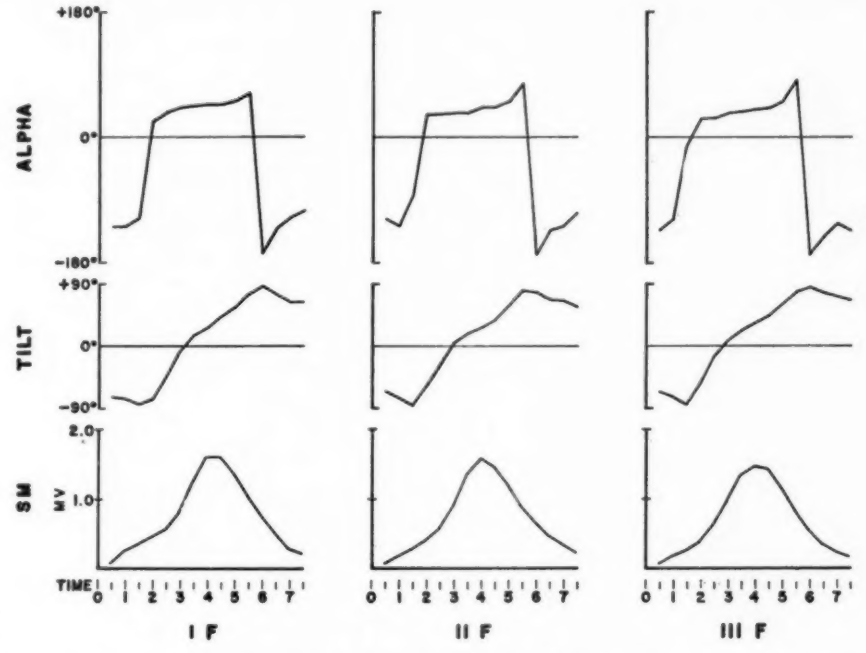

Fig. 7.—Simultaneous representation of the mean values of alpha, tilt, and spatial magnitude. Female groups.

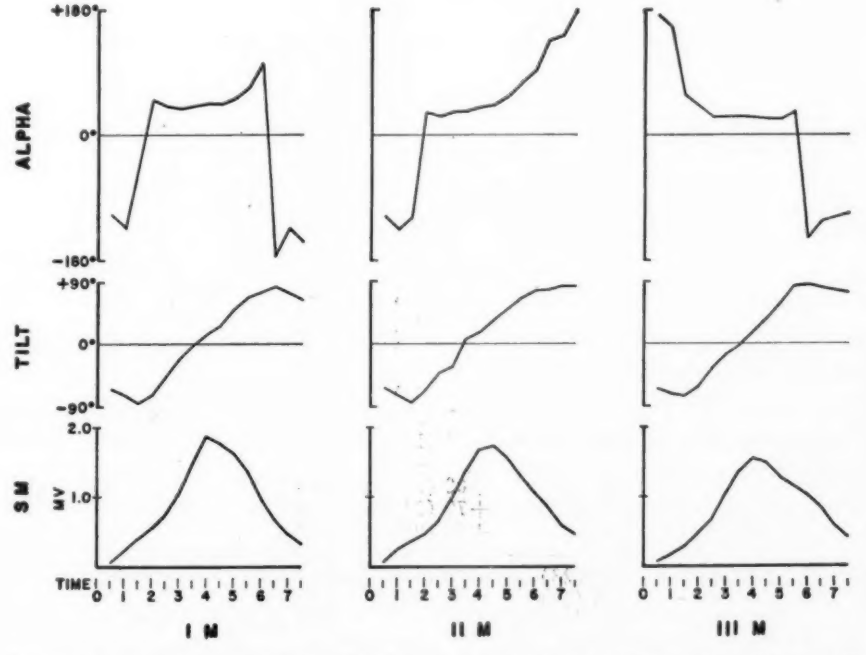

Fig. 8.—Simultaneous representation of the mean values of alpha, tilt, and spatial magnitude. Male groups.

TABLE II. MEAN AND STANDARD DEVIATION VALUES OF ALPHA (IN DEGREES)

MSEC.	GROUP					
	1F	2F	3F	1M	2M	3M
5	−129 (66)	−117 (66)	−131 (62)	−114 (54)	−118 (48)	+172 (69)
10	−128 (67)	−127 (75)	−118 (76)	−131 (62)	−135 (58)	+154 (66)
15	−115 (92)	−81 (98)	−12 (96)	+167 (95)	−120 (93)	+59 (90)
20	+23 (93)	+32 (56)	+26 (56)	+50 (84)	+31 (69)	+42 (40)
25	+36 (32)	+32 (16)	+29 (23)	+43 (46)	+28 (18)	+26 (21)
30	+42 (13)	+35 (13)	+33 (12)	+39 (9)	+33 (12)	+27 (11)
35	+46 (12)	+39 (13)	+37 (13)	+43 (12)	+35 (12)	+26 (12)
40	+48 (13)	+43 (16)	+40 (18)	+46 (11)	+40 (12)	+26 (24)
45	+49 (25)	+45 (28)	+42 (35)	+47 (18)	+44 (21)	+24 (47)
50	+51 (59)	+51 (58)	+52 (61)	+53 (35)	+56 (43)	+24 (71)
55	+63 (84)	+79 (86)	+81 (78)	+69 (73)	+75 (50)	+31 (102)
60	−164 (93)	−167 (75)	−167 (90)	+101 (73)	+93 (73)	−146 (100)
65	−130 (83)	−131 (57)	−143 (77)	−174 (86)	+132 (75)	−124 (88)
70	−112 (73)	−125 (78)	−122 (84)	−132 (79)	+142 (85)	−119 (83)
75	−106 (85)	−109 (71)	−131 (80)	−151 (78)	+178 (95)	−112 (84)

Figures in parentheses denote standard deviation.

TABLE III. MEAN AND STANDARD DEVIATION VALUES OF TILT (IN DEGREES)

MSEC.	GROUP					
	1F	2F	3F	1M	2M	3M
5	−73 (23)	−64 (32)	−66 (20)	−65 (30)	−64 (21)	−66 (23)
10	−75 (24)	−75 (25)	−73 (16)	−73 (18)	−73 (15)	−71 (20)
15	−83 (19)	−87 (33)	−85 (29)	−85 (24)	−85 (23)	−76 (26)
20	−77 (17)	−58 (19)	−53 (25)	−73 (21)	−69 (25)	−63 (28)
25	−44 (19)	−29 (22)	−16 (27)	−48 (25)	−43 (26)	−38 (18)
30	−9 (21)	+1 (20)	+7 (21)	−21 (30)	−32 (32)	−17 (30)
35	+15 (13)	+19 (18)	+21 (18)	−1 (24)	+5 (19)	−2 (21)
40	+27 (10)	+27 (17)	+32 (17)	+13 (21)	+19 (17)	+17 (20)
45	+41 (16)	+38 (17)	+44 (17)	+27 (19)	+33 (17)	+35 (22)
50	+57 (19)	+59 (20)	+60 (20)	+49 (21)	+50 (17)	+57 (21)
55	+76 (23)	+80 (25)	+78 (24)	+67 (24)	+65 (19)	+81 (26)
60	+87 (30)	+78 (23)	+85 (26)	+75 (25)	+76 (17)	+85 (24)
65	+75 (26)	+67 (23)	+78 (28)	+81 (28)	+78 (17)	+80 (25)
70	+64 (35)	+65 (28)	+72 (50)	+75 (41)	+82 (31)	+77 (30)
75	+65 (48)	+56 (36)	+67 (43)	+64 (45)	+81 (36)	+73 (29)

Figures in parentheses denote standard deviation.

TABLE IV. MEAN AND COEFFICIENT OF VARIATION VALUES OF THE SPATIAL MAGNITUDE (IN MILLIVOLTS)

MSEC.	GROUP					
	1F	2F	3F	1M	2M	3M
5	.09 (55)	.07 (71)	.07 (57)	.08 (71)	.07 (71)	.07 (43)
10	.23 (56)	.19 (53)	.19 (42)	.21 (48)	.23 (52)	.17 (35)
15	.35 (37)	.28 (53)	.28 (36)	.40 (42)	.35 (43)	.29 (45)
20	.45 (42)	.40 (40)	.38 (45)	.54 (35)	.45 (38)	.45 (33)
25	.54 (35)	.57 (33)	.63 (41)	.73 (35)	.64 (37)	.66 (39)
30	.80 (41)	.90 (30)	.97 (37)	1.04 (32)	.96 (34)	1.01 (33)
35	1.25 (34)	1.36 (25)	1.32 (30)	1.49 (27)	1.37 (30)	1.35 (33)
40	1.60 (28)	1.58 (21)	1.48 (28)	1.88 (21)	1.67 (25)	1.53 (35)
45	1.60 (24)	1.48 (31)	1.43 (30)	1.79 (33)	1.72 (28)	1.49 (33)
50	1.36 (34)	1.20 (43)	1.15 (33)	1.63 (34)	1.56 (31)	1.28 (30)
55	1.04 (46)	.90 (42)	.82 (40)	1.39 (36)	1.30 (31)	1.14 (38)
60	.76 (61)	.68 (53)	.56 (48)	.97 (42)	1.06 (41)	1.01 (48)
65	.50 (72)	.49 (59)	.36 (55)	.68 (43)	.82 (52)	.83 (54)
70	.29 (89)	.35 (63)	.24 (54)	.47 (56)	.59 (64)	.59 (64)
75	.21 (90)	.21 (62)	.17 (59)	.31 (55)	.45 (64)	.42 (74)

Figures in parentheses denote coefficient of variation.

TABLE V. MEAN AND STANDARD DEVIATION VALUES OF THE POLAR VECTOR (IN DEGREES)

	GROUP					
	1F	2F	3F	1M	2M	3M
Alpha	−45 (10)	−50 (13)	−51 (12)	−47 (14)	−54 (15)	−63 (14)
Tilt	+6 (16)	+12 (19)	+7 (18)	+8 (19)	+12 (17)	−1 (17)

Figures in parentheses denote standard deviation.

DISCUSSION

The wide range of individual variation observed in the normal electrocardiogram and also in the normal plane projection vectorcardiograms led to the question whether it would be possible to understand these variations as a function of a hidden parameter. The roentgenologic variations in the position of the heart suggested that the normal variations of the electrocardiogram could be explained by such positional variations seen in normal individuals. Theoretically, this means that if we were able to bring all normal hearts into the same position within the chest, all electrocardiograms or plane projection vectorcardiograms of normal individuals would look alike. We are at this time purposely ignoring the problem of orthogonality of the lead system and assume that the heart is in the center of our reference system. The theory of Ashman[9,10] sought to explain

the electrocardiographic variations as a positional rotation. $S_1 - Q_3$, $Q_1 - S_3$, and other types were considered to be the result of an anatomic rotation about the anterior-posterior, longitudinal, and transverse axes.[11] It was soon found that in order to explain the considerable variations, seen in the electrocardiogram of normal individuals, anatomic rotations of such an extent were required which are ordinarily not observed either in autopsy or in angiocardiographic findings. Milnor[8] introduced a new parameter, namely, the QRS plane of Schellong, also called the plane of predilection. This plane is located by rotating the spatial loop with the panoramic unit into an edge position. The plane perpendicular to the edge projection is the plane of predilection, and the projection of the spatial QRS loop into the latter is called the open plane projection. We rotate, so to speak, our instrument into the plane of the individual loop and thereby cancel the rotational variations present in a rigid reference frame. Milnor emphasizes that the variations of the individual rotation of the plane of predilection should not be understood as anatomic rotations, but might find their explanation in the variations in the structure of the ventricles and the sequence of the myocardial activation. He demonstrates that the QRS loops of the open plane projection have less individual variations than do the QRS loops in the conventional plane projections.

The concept of the QRS plane used by Milnor lacks, as he states, a sharp mathematical definition, because the loop has to be rotated until a maximum major/minor ratio is found. Deviations from the plane are therefore disregarded in his concept of the plane position. Burger and Vaane[3] introduced a new, mathematically well-defined concept of the plane, namely, the polar vector. This is the unit normal vector to the surface of the mean plane as calculated from the three integrals of the areas of the projection of the spatial QRS loop on the coordinate planes. This concept of the QRS plane was used in our investigations, and deviations from the plane as well as open plane projections were determined with reference to it. If all normal loops were more or less congruent figures, then the apparent incongruence could only be due to variations in the position of the QRS plane within our reference frame. When we speak of congruence, we have to consider time as well as space. Two QRS loops could have spatial congruence without having temporal congruence. Even if all normal loops lay in a perfect plane, individual variations could still exist as soon as we view the electrical signal of the heart as a function of time. These variations cannot be cancelled by any kind of rotation. The same is true for variations in the absolute vector magnitude, here called spatial magnitude, which is invariant to position. Therefore, if we ask for the cause of the wide variations in the appearance of the normal electrocardiogram and also the plane projection vectorcardiogram, the distinction between variations which are caused by the relation of the loop to our reference system and variations within the structure of the loop independent of the reference system is of importance. The former encloses anatomic rotations as well as those variations which are thought to be responsible for the position of the plane of predilection within the system; the latter refers to such quantities as the angular velocity, the deviation from the plane of predilection, and the spatial magnitude, which are independent of the reference system.

How are the results of our investigation related to these findings? We have a simultaneous recording of the spherical coordinates of each individual (Fig. 3), and these were plotted into angular frequency distribution charts (Figs. 4-6). Our reference system is the surface of a sphere (Fig. 2). When we refer to spatial magnitudes, these vectors may be pictured as projecting radially from the surface of the sphere, having a length equal to the spatial magnitude. Our reference system is fixed, and not, like the open projection of Milnor, moved into the individual QRS plane. The values of alpha and tilt represent a point on the sphere, indicating the spatial direction of the vector. The frequency distribution charts or scattergrams were made to visualize the spherical distribution as a function of time. How can we explain the wide scatter over the anterior four octants during the time interval of 0 to 20 msec., over the posterior four octants during the interval of 55 to 75 msec., and in contrast to it the minimal dispersion between 30 and 45 msec.? What are the governing factors responsible for this difference in individual variation which becomes so apparent when we view the direction vector as a function of time? Is it possible to think that individual variations in anatomic position could explain our findings? Rotations about the anterior-posterior axis which determine the roentgenologic angle α are found to be in the range of $+20°$ to $+90°$. This coincides well with the range of dispersion seen in the scattergrams during the time interval of 30 to 45 msec., but would certainly not explain the wide scatter of the initial and terminal sections. Could rotations about the longitudinal axis be responsible for this? The anatomic cardiac axis and the mean axis of the maximal instantaneous vector do not coincide in their spatial orientation. Both run from right above to left below, but the anatomic axis has a forward tilt, and the axis of the maximal vector has a backward tilt. When we consider the rotation about the longitudinal axis, we must distinguish these two axes. Not very much is known about the range of rotation about the longitudinal anatomic axis, but according to angiocardiographic observations, it is not to exceed 25 degrees on either side. Schweizer[12] found in his experiments that a rotation about the longitudinal axis resulted in very minor changes in the frontal plane leads, as long as the original position of the QRS vector was parallel to the frontal plane. If this was not the case, the same rotation led to noticeable variations in the same leads. This is easily understood because vectors which run more nearly parallel to the axis of rotation will be less affected in their spatial direction than will those that have a large angle of inclination against the axis of rotation. This may explain in part why we see such a wide scatter during the first 20 msec. and again during the terminal 25 msec., the former having large forward tilts, the latter having large backward tilts. But the range of the scatter of the polar vectors observed by Burger, as well as by us, makes it difficult to believe that anatomic rotations could explain the variations seen in the position of the plane of predilection. We have to assume, therefore, as Milnor did, that the position of the plane of predilection is determined by a set of factors, only one of which is the anatomic. Is this then the solution of the problem of the wide range of individual variation observed in the normal electrocardiogram and vectorcardiogram?

Duchosal[13,14] observed in his wire models a considerable incongruence even if they were brought into the plane of predilection, and this incongruence was

more pronounced during the initial and terminal portions than during the peak region of the spatial magnitude. For Group 1F, we rotated all spatial loops by means of a mathematical calculation (orthogonal transformation) into the open plane projection. Here all QRS loops are seen in their own plane given by their polar vector, and their own reference axis given by the direction of the instantaneous maximal vector. If the parameter of the plane of predilection was the solution of all normal individual variations, then there would be little or no scatter in this diagram (Fig. 9). This is not the case. The scatter of this diagram demonstrates the fact that in addition to variations caused by the relation of the loop to our reference system there are variations of a truly inherent nature which cannot be resolved by a rotation of our reference system. They are, as we can see in the scattergram of Fig. 9,*A* and *B*, more pronounced during the initial and terminal portions than during the central section.

The pattern of our angular frequency distribution finds its explanation, therefore, in rotational variations, anatomic or otherwise, as well as in truly

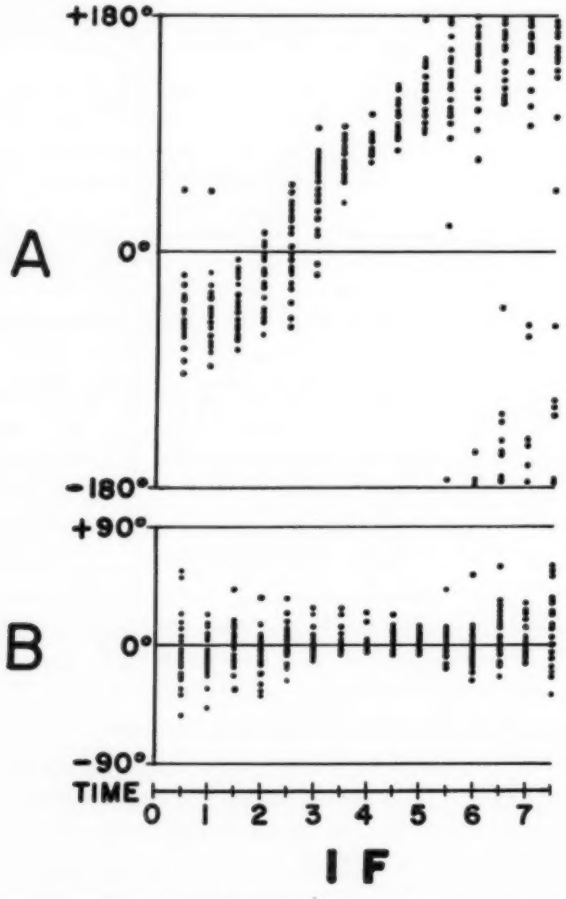

Fig. 9.—Angular distribution in the open plane projection. *A*, Direction angles of the instantaneous vector projected into the open plane, plotted for 25 individuals of Group 1F. The distribution represented in this diagram uses the individual QRS plane as viewed on the caudad surface as reference plane. *B*, Deviation of the instantaneous vector from the QRS plane. The QRS plane is given by the polar vector. Deviations are either toward (+) or away (−) from the polar vector.

individual structural variations. Either factor may be predominant. By superimposing the graphs of the spherical coordinates of any individual upon the angular distribution chart (scattergram) of the respective age group (Fig. 10), we can see that deviations from the mean during the first 15 msec. are not significant unless they are found to be in the abnormal region of the tilt chart. The same holds true for the time interval of 55 to 70 msec. This is different during the time interval of 25 to 50 msec., wherein the individual variation is not so wide, and especially between 30 and 45 msec., wherein the zone of dispersion has its minimal range. This zone of minimal variability does not overlap symmetrically with the peak region of the mean spatial magnitude curve, but coincides with the last 10 or 15 msec. of the ascending branch of this curve. One explanation of this asymmetry is that the direction vectors at 30 msec. are more nearly parallel to the anatomic longitudinal axis and therefore less affected by a rotation about this axis than are the vectors at 50 msec., which have a marked backward tilt. It is also possible that the asymmetry is not related to rotational variations, but that we are at the time interval of 30 to 45 msec. in the possession of the most uniform representation of the activation wave front.

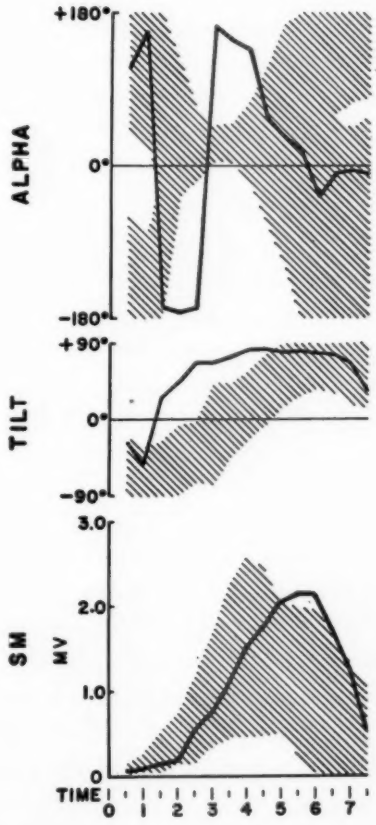

Fig. 10.—Alpha, tilt, and spatial magnitude graph of a 49-year-old man who suffered an anterolateral infarction. The graph is superimposed upon the distribution chart of his age group (3M). The shaded area represents the value $\bar{\alpha} \pm 2s$, $\bar{T} \pm 2s$, $\bar{SM} \pm 2s$, where s = standard deviation. The probability of a value falling outside the shaded region is 0.045.

Since considerable individual variations in the normal spatial loop exist which cannot be resolved by rotation of the reference system, and since these variations may in some individuals, especially during the initial and terminal portions of the loop, be the predominant factor, it is a question whether open plane projections of the loop will be of great diagnostic value other than for determining the position of the plane, which in our case was done by the simple method introduced by Burger. The fixed reference system and the recording of the spherical coordinates on a linear time base against the background of the normal distribution is thought by us to have a greater discriminating power, particularly in the regions of minimal dispersions, which were established in this investigation. The process of establishing such a calibration background as attempted in this study is tedious and its method involved. Abildskov[15] records angular and spatial magnitude values directly on a linear time base and thereby eliminates the conversion which in our case had to be done with the aid of a vector coordinator and tabulated functions. Large-scale studies will undoubtedly have to be done with the aid of high-speed electronic computers, but once reliable calibration curves, with proper consideration of age, sex, and perhaps other significant factors, have been established, the testing of an individual against such a background will be simple and perhaps provide us with a better definition of the range and limitations of vectorcardiographic diagnosis. An unwarranted exactitude must be avoided, of course, and variations observed between different lead systems,[16,17] which are purposely ignored in this investigation, will also have to be taken into consideration.

SUMMARY

The spatial distribution of the QRS complex of 154 normal individuals was analyzed in this investigation. The three scalar vector components X, Y, and Z were recorded simultaneously at high speed on film, and the Lissajous loops of the three body planes were displayed on the cathode-ray oscilloscope. The spherical coordinates of the instantaneous vectors were determined from the time-based scalar recordings with the aid of a vector coordinating instrument and tabulated functions. The data obtained were plotted into charts, representing the angular distribution as a function of time. The position of the polar vector, representing the spatial orientation of the principal QRS plane, was calculated from plane projection areas. Mean and standard deviation values of the spherical coordinates of the instantaneous as well as the polar vectors were determined for all individuals. The wide range of individual variability observed during the initial and terminal portions of the QRS complex is not fully explained by rotation, anatomic or otherwise. An inherent structural variation was demonstrated by viewing plane deviations and open plane projection vectors as a function of time. Individual scatter is narrow during the time of the peak and for a short interval preceding it. This region of minimal dispersion appears to be of value for comparative studies. There are during this interval well-defined, consistent differences between the male and female groups, as well as between the respective age groups. The group of men between the age of 40 and 50 shows a more marked change

than does the corresponding female group. The region defined by the mean and standard deviation values of the spherical coordinates can be plotted as a function of time and serve as a calibration curve against which individual tracings may be tested. More extensive studies and clinical correlation will be necessary before the discriminating power of this method can be fully evaluated.

I wish to thank Dr. M. Juncosa, of the Rand Corporation, for his helpful advice, and Mr. Harry Stern, of the Allegany Instrument Company, for his support of this project.

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Graphic Determination and Comparison of RLF Plane Vector Angles Obtained From Lead Projection Ratios Using the Einthoven and Various Burger-Type Triangles

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The scalene triangle of Burger and van Milaan[1-3] based on the concept of the lead vector is gaining increasing acceptance as a more rational reference frame than the Einthoven equilateral triangle for the determination of RLF plane vector angles, since it attempts to provide for such factors as variability of cardiac anatomic position, heterogeneity of thoracic tissue resistance, and irregularity of body contour.

Although it is probable that each individual should, in fact, have his own characteristic scalene reference frame, a "mean triangle" which has been regarded as most nearly applicable to the general population was determined by Burger and van Milaan from studies on synthetic torsos and cadavers, and this has been assumed to represent with reasonable accuracy the quantitative relationships between the electromotive forces of the heart and the extremity leads. Brody and Romans[4] have extended the theoretical studies on the lead vector and its graphic presentation, and Brody[5] has described a method for transforming the Burger triangle into a coordinate system which obeys the Einthoven law.

The RLF plane cardiac vector angle or "electric axis" is customarily determined from the resultant of the projections on to any two lead axes of the equilateral triangle, the magnitudes of the projections having been estimated from the heights of electrocardiographic scalar complexes or, more accurately, from the algebraically summated areas enclosed by the complexes. It is apparent that, when attention is paid to conventional polarities, each vector angle is characterized by specific ratios of lead projections on to any given reference frame irrespective of vector magnitude. The ratios for each angle will obviously vary with different reference systems, but for any system it is a simple mathematical exercise to tabulate the lead projection ratios for all angles of the RLF plane in order subsequently to determine by inspection the vector angle as given by a particular reference frame for any individual set of scalar limb lead tracings.

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Received for publication Nov. 2, 1959.

The relationships of the angles obtained by plotting an arbitrary vector on the Einthoven and various Burger triangular systems were studied qualitatively by Zao,[6] who observed that the more the triangle departs from the equilateral form the more the direction of the vector deviates from that given by the Einthoven triangle. Consequently, it appeared to be of interest and importance to study more quantitatively these relationships for a wider range of scalene triangles, particularly since it was desired later to make comparisons between the frontal plane vector angle as derived from the lead field technique[7] and the RLF plane angle as determined from limb lead data.

It was decided, therefore, first to calculate and present in graphic form the three limb lead projection ratios for Lead I to Lead II, I to III, and II to III, and their corresponding vector angles as given by the equilateral and four representative scalene triangular reference frames, in order to extend the data of Zao, who previously published selected ratios of Lead I to III for the Einthoven[8] and the "mean" Burger triangle.[9]

From analysis of the results of these calculations it was observed that some important deductions could be drawn concerning the interrelationships between the vector angles as derived from the different reference systems and the manner in which they varied with change in electric axis as indicated by the traditional Einthoven triangle. Some of these deductions are discussed hereinafter.

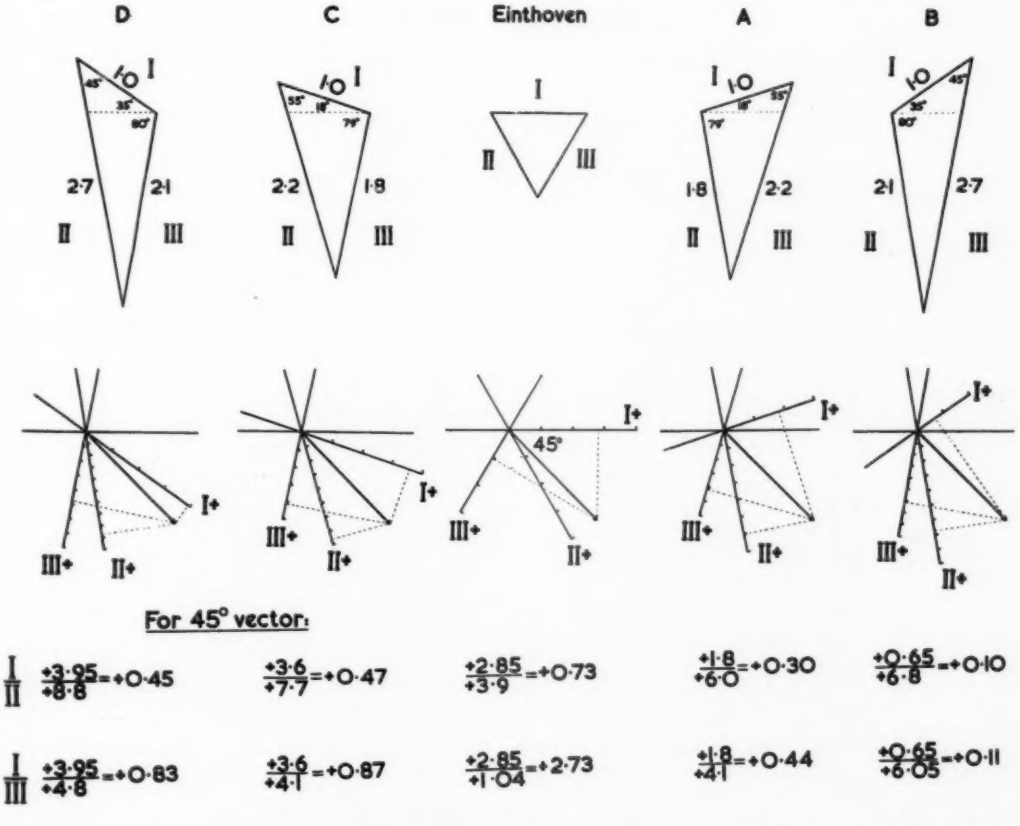

Fig. 1.—Five triangular reference frames selected for study, with lead ratios for an arbitrary vector angle of 45°.

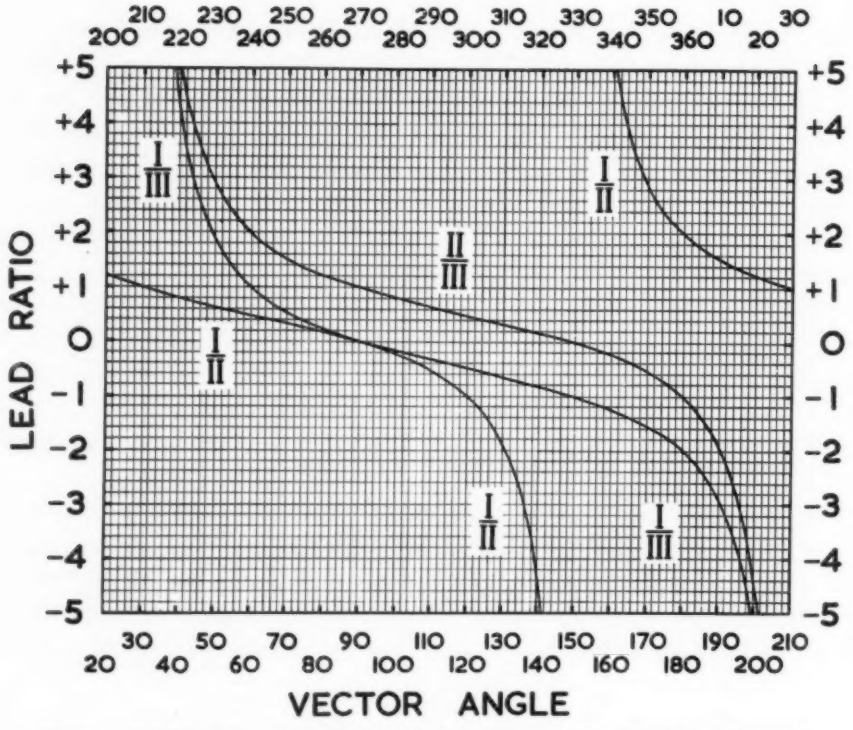

Fig. 2.—Relation between lead ratio and vector angle for Einthoven triangle.

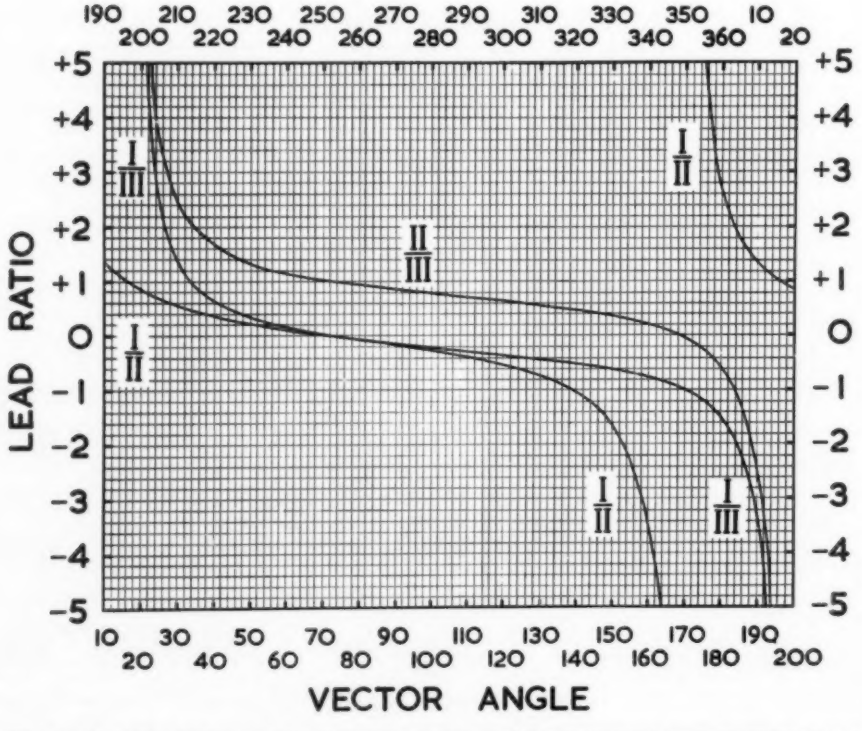

Fig. 3.—Relation between lead ratio and vector angle for "mean" Burger triangle (A).

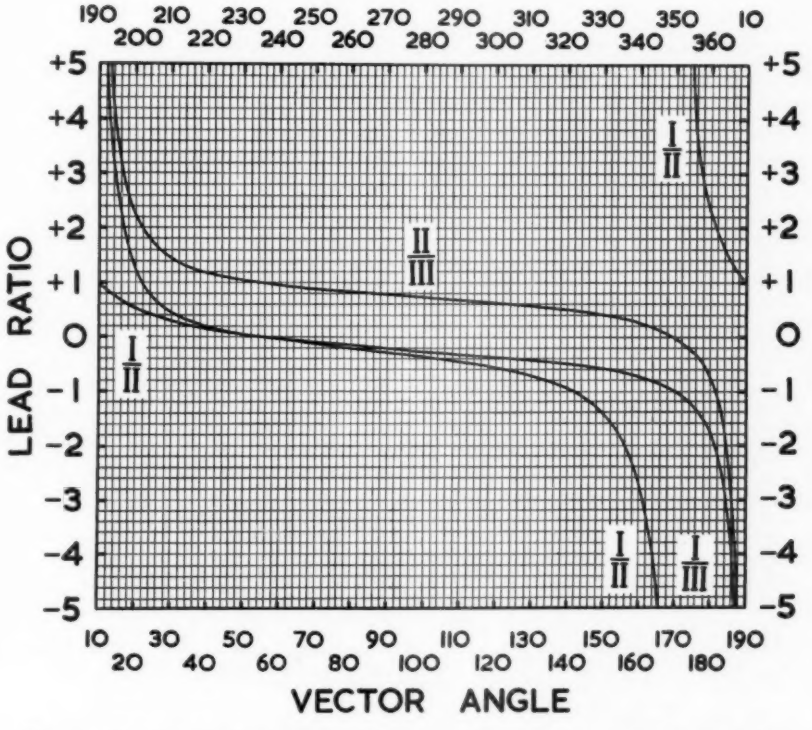

Fig. 4.—Relation between lead ratio and vector angle for scalene triangle B.

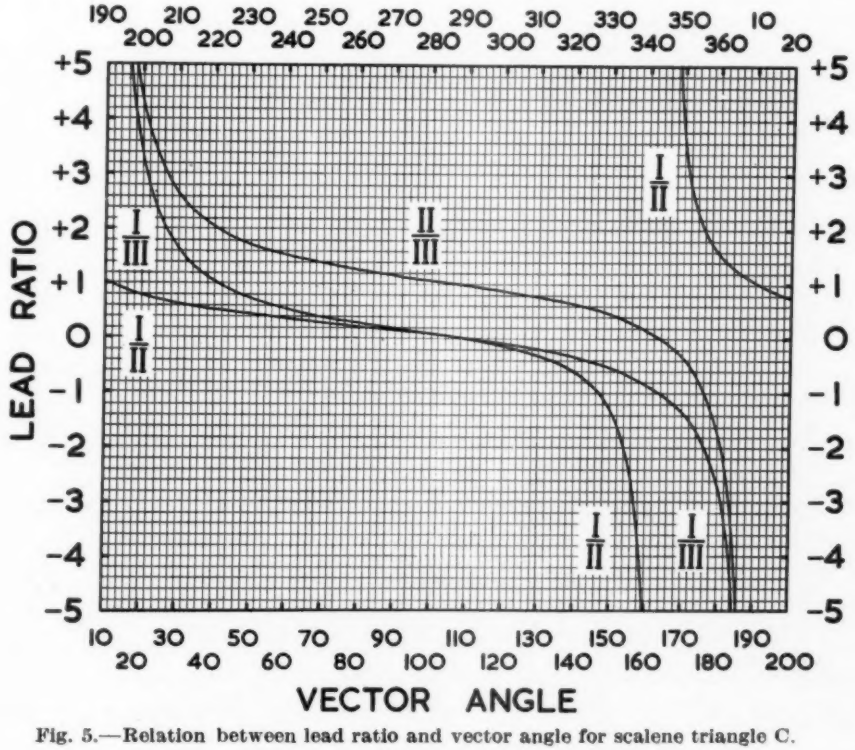

Fig. 5.—Relation between lead ratio and vector angle for scalene triangle C.

METHOD

The triangles chosen for investigation and their corresponding hexaxial frames are shown in Fig. 1. They consist of the Einthoven (equilateral) triangle, "mean" Burger triangle (A) as described by Zao,[9] a scalene triangle B with a more vertical Lead I axis, and triangles C and D, which are the mirror-images of A and B, respectively.

The trigonometric method used by Zao for the calculation of the ratio of Lead I to III for any vector angle on the equilateral triangle has been applied to all three lead ratios for all five selected triangles after appropriate calibration of the axes of the scalene hexaxial reference frames as suggested by Brody and Romans.[4] According to these authors, each axis must be calibrated in unit lengths which are inversely related to the lengths of the sides of the triangles. For example, in the case of the "mean" Burger triangle (A) in which the lengths of the sides bear the proportions I: II: III:: 1.0 : 1.8 : 2.2, the length of each unit along the Lead II axis must be equal to the Lead I unit divided by 2.2. When these calibrations have been made, the lead projection ratios for any vector can be determined by direct measurement of perpendicular intercepts on to the leads, as illustrated for a vector angle of 45° in Fig. 1 or, more accurately, by trigonometry.

If, in any scalene triangle, the angles between the lead axes be designated ∠ (I) (II), ∠ (I) (III), and ∠ (II) (III), respectively, and θ be the angle that the Lead I axis makes with the horizontal, then for any vector angle α we have:

$$\frac{\text{Lead I}}{\text{Lead II}} = \frac{\cos(\alpha+\theta) \times \text{length of side I}}{\cos[\angle(\text{I})(\text{II}) - (\alpha+\theta)] \times \text{length of side II}}$$

$$\frac{\text{Lead I}}{\text{Lead III}} = \frac{\cos(\alpha+\theta) \times \text{length of side I}}{\cos[\angle(\text{II})(\text{III}) + \angle(\text{I})(\text{II}) - (\alpha+\theta)] \times \text{length of side III}}$$

For each triangle the three lead ratios at 5° intervals were calculated in this manner for the whole 360° of the RLF plane. As an example of the method for the arbitrary vector angle of 45° with the horizontal we have:

Reference frame	$\frac{\text{Lead I}}{\text{Lead II}}$			$\frac{\text{Lead I}}{\text{Lead III}}$		
Einthoven	$\frac{\cos 45°}{\cos 15°}$	$= \frac{+0.7071}{+0.9659}$	$= +0.73$	$\frac{\cos 45°}{\cos 75°}$	$= \frac{+0.7071}{+0.2588}$	$= +2.73$
Triangle A	$\frac{\cos 63°}{\cos 34° \times 1.8}$	$= \frac{+0.4540}{+0.8290 \times 1.8}$	$= +0.30$	$\frac{\cos 63°}{\cos 62° \times 2.2}$	$= \frac{+0.4540}{+0.4695 \times 2.2}$	$= +0.44$
Triangle B	$\frac{\cos 80°}{\cos 35° \times 2.1}$	$= \frac{+0.1736}{+0.8192 \times 2.1}$	$= +0.10$	$\frac{\cos 80°}{\cos 55° \times 2.7}$	$= \frac{+0.1736}{+0.5736 \times 2.7}$	$= +0.11$
Triangle C	$\frac{\cos 27°}{\cos 28° \times 2.2}$	$= \frac{+0.8910}{+0.8829 \times 2.2}$	$= +0.47$	$\frac{\cos 27°}{\cos 56° \times 1.8}$	$= \frac{+0.8910}{+0.5592 \times 1.8}$	$= +0.87$
Triangle D	$\frac{\cos 10°}{\cos 35° \times 2.7}$	$= \frac{+0.9848}{+0.8192 \times 2.7}$	$= +0.45$	$\frac{\cos 10°}{\cos 55° \times 2.1}$	$= \frac{+0.9848}{+0.5736 \times 2.1}$	$= +0.83$

RESULTS

The vector angles corresponding to the projection ratios $\frac{\text{Lead I}}{\text{Lead II}}$, $\frac{\text{Lead I}}{\text{Lead III}}$, and $\frac{\text{Lead II}}{\text{Lead III}}$ are given in Figs. 2 to 6. It is apparent that the scalene triangles

yield curves which become flatter over their middle ranges the more the triangle deviates from the equilateral form, and that the vector angle corresponding to a ratio of zero for $\frac{\text{Lead I}}{\text{Lead II}}$ and $\frac{\text{Lead I}}{\text{Lead III}}$ decreases progressively from triangle D to triangle B, the angle differing from 90° by an amount equal to the elevation of Lead I above the horizontal.

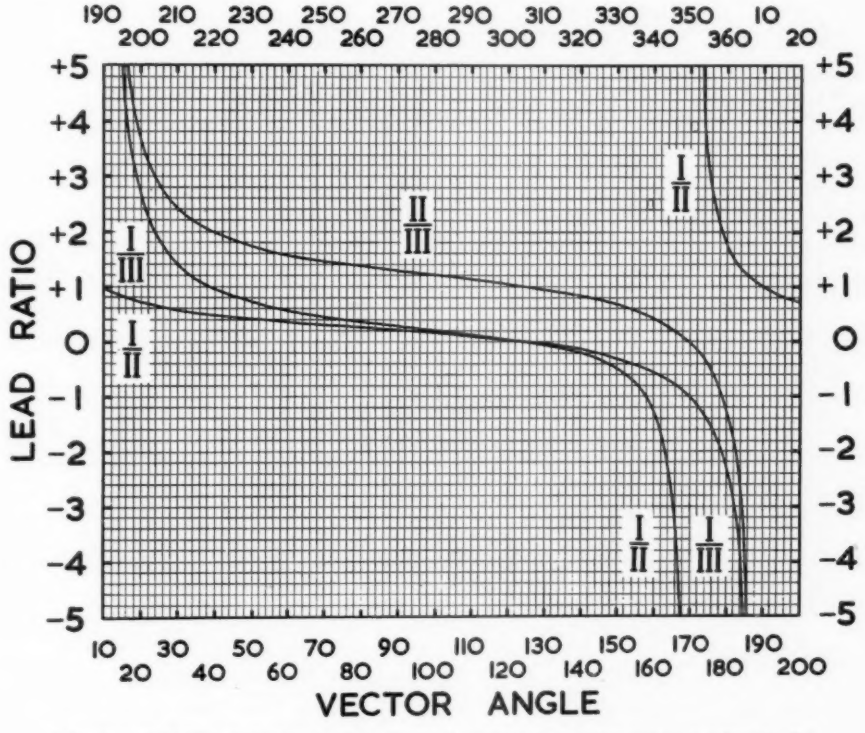

Fig. 6.—Relation between lead ratio and vector angle for scalene triangle D.

To demonstrate the relationships between the angles as given by the various reference frames for a series of arbitrary vectors, the lead ratios for Einthoven angles at 10° intervals from 0° to 180° were selected and the corresponding vector angles for the scalene triangles determined from Figs. 2 to 6. In this way, for each ratio a group of five angles is obtained, and these are shown diagrammatically for $\frac{\text{Lead I}}{\text{Lead II}}$ in Fig. 7. For example, at an Einthoven angle of 60° the ratio is +0.50, which corresponds to angles of 34°, 22°, 41°, and 39° for triangles A, B, C, and D, respectively.

The same angular relationships as those shown in Fig. 7 are given by all three pairs of leads, and it is obvious that at each lead ratio the equilateral triangle gives a vector angle which is, in general, more vertical than that for any of the scalene triangles investigated, and that the more eccentric the reference frame the more horizontal is the derived angle. Also, whereas the Einthoven intervals were selected as constant at 10°, the corresponding scalene triangle intervals vary systematically.

A direct comparison of the vector angles as given by all five reference frames and applicable to any of the three lead ratios over the whole range of 0° to 360° is shown in Fig. 8.

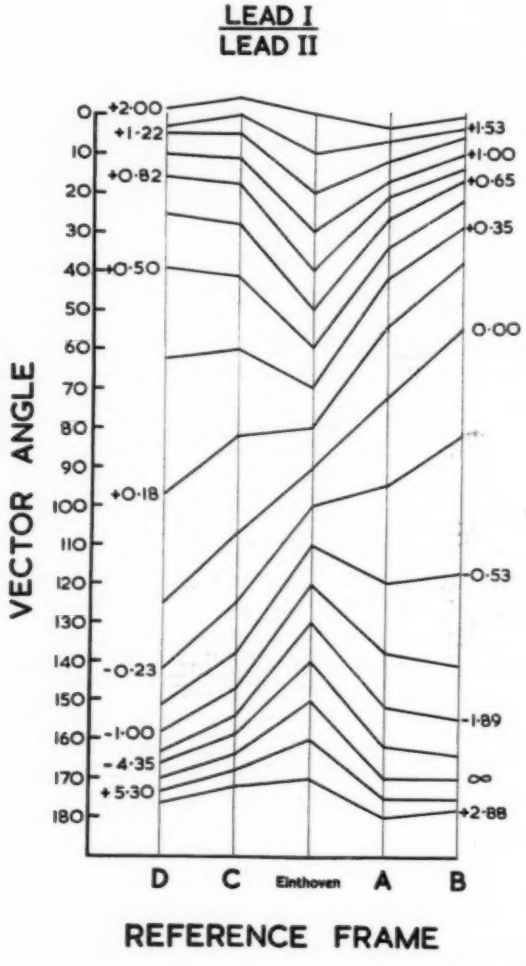

Fig. 7.—Relation between vector angles derived from five reference frames for selected $\frac{\text{Lead I}}{\text{Lead II}}$ ratios.

DISCUSSION

Much has been written in recent years concerning the merits of the Burger scalene triangle as a more appropriate reference frame than the Einthoven equilateral from which to compute the RLF plane vector angle. But no comprehensive analysis appears to have been made of the quantitative relationship which the RLF vector angle, as customarily calculated for the "electric axis" of the heart, bears to the corresponding axes derived from scalene triangles of the type recommended by Burger and van Milaan.

The only previous attempt to relate these angles was that of Zao,[6] who showed that a lead ratio corresponding to 45° on the Einthoven scale gave in

each of a series of scalene triangles (in which the Lead I axis was represented by the shortest side) an angle smaller than 45°.

The results reported here confirm and extend this observation. From Fig. 7 it is apparent that in the 0° to 90° quadrant the Einthoven angles are greater than the corresponding scalene values in the range of 10° to 70°, i.e., the Einthoven vector is always placed more vertically. Similarly, in the 90° to 180° quadrant, although in the range of 110° to 170° the Einthoven value is smaller than the scalene, this, in fact, also represents a more vertical orientation of the equilateral vector. Around the value of 90° on the Einthoven scale there is obviously a region in which this simple relationship no longer holds, since the scalene-derived axes pass through the 90° point out of phase.

It is of interest to note that the scalene triangle A, which is the so-called "mean" Burger triangle that has been advocated as being superior to the Einthoven for general applicability, yields more horizontal vector angles than the equilateral over the whole 0° to 180° range, except for a very limited interval between 95° and 103°.

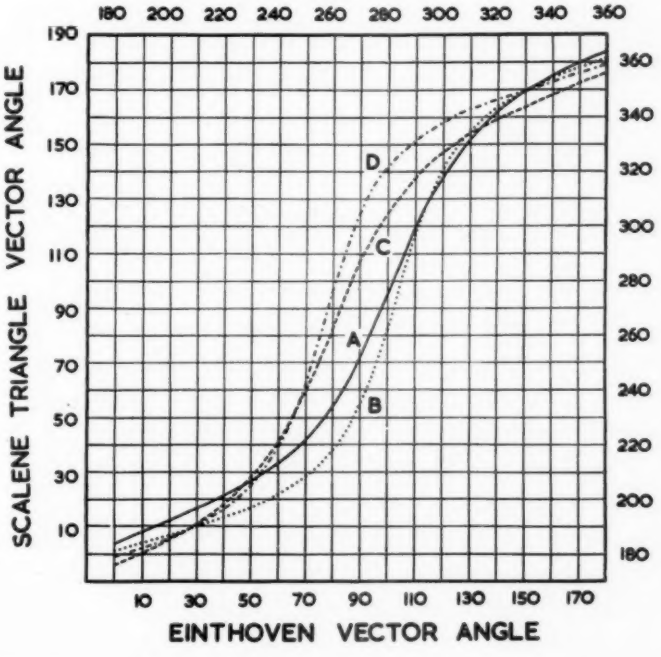

Fig. 8.—Relation between Einthoven vector angle and those given by scalene triangles A, B, C, and D.

From Fig. 8, which compares directly the interrelationships between the vector angles as calculated from the various triangles, it is seen that the differences between the equilateral and scalene values vary continuously throughout the 360° of the RLF plane. In hearts having electrically horizontal axes, all five methods of assessment give essentially similar values, i.e., within ±4°. Within the range of Einthoven values from 0° to 50° the "mean" Burger triangle (A) values are approximately linearly related to the Einthoven angles and lie closer

to the latter than do those of the other three scalene reference frames; but in the important normal clinical range of 50° to 80°, triangles A and B produce maximal discrepancies from the equilateral values, whereas triangles C and D, which are usually regarded as having less physiologic significance, give values which agree much more closely with those of Einthoven. Between 80° and 90° the pairs of triangles A and B and C and D yield differences from Einthoven which are approximately equal in magnitude but opposite in sign.

The angular difference between QRS and T in the RLF plane has frequently been used as a criterion by which to assess the degree of cardiac electric rotation on a longitudinal axis. This approach is, however, open to considerable criticism. Even if it is assumed that in any given individual the same reference system is appropriate to both depolarization and repolarization phenomena, it should be emphasized that the apparent QRS-T angle is a function of the reference frame used. In hearts having more horizontal vectors it may be deduced from Fig. 7 that the Einthoven QRS-T angle is greater than that given by any of the scalene triangles, whereas in vertical hearts the reverse is the case. In the intermediate region the Einthoven angles are greater than those of triangles A and B but less than those of C and D. The apparent degree of longitudinal rotation, if deduced from RLF plane QRS-T angles, obviously depends, therefore, not only on the particular reference frame but also on the quadrantal positions of the individual vectors.

SUMMARY

The limb lead projection ratios for $\frac{\text{Lead I}}{\text{Lead II}}$, $\frac{\text{Lead I}}{\text{Lead III}}$, and $\frac{\text{Lead II}}{\text{Lead III}}$ throughout the 360° of the RLF plane have been presented for the Einthoven and four representative Burger-type scalene triangular reference frames.

Comparison of the angles given by the various reference systems for each lead ratio showed that, although in hearts having electrically horizontal axes all five methods of assessment gave essentially similar angular values, the vector as determined from the equilateral triangle is, in general, placed more vertically than by any of the scalene triangles.

Within the range 0° to 50° the "mean" Burger triangle produced angles nearest to the Einthoven values, but in the clinically important range of 50° to 80° gave maximal differences from the Einthoven.

The angular difference between QRS and T in the RLF plane is shown to be a function of the reference frame used and, consequently, should not be employed as a measure of cardiac electric longitudinal rotation unless the individual's own characteristic reference system can be determined.

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Case Report

Biventricular Transposed Aorta and Left Ventricular Stenotic Pulmonary Artery. An Embryologic and Pathologic Account of a New Syndrome Whose Existence Was Previously Theoretically Predicted

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INTRODUCTION

This paper deals with a new variety of transposition of the great vessels, the anatomic picture of which had been anticipated in an embryologic theory on truncoconal malformations recently published by one of us.[4]

Left ventricular hypertrophy is unusual in transposition of the great vessels. This feature seems to be the result of a biventricular aorta and a narrow pulmonary artery arising from the left ventricle. Therefore, the clinical and electrocardiographic data differ from those classically described for complete transposition of the great vessels.

REPORT OF A CASE

S.R., a 22-year-old male patient, was known to have been cyanotic since birth, especially evidencing cyanosis after physical effort. During childhood he adopted the squatting position occasionally. Cyanosis gradually increased with age. Hypoxic spells began to appear from the time he was 17 years old. Physical development, however, was normal, and up to the age of 18 years he had no limitation of activity. About that time, heart failure began to appear.

Physical examination disclosed a well-developed, markedly cyanotic individual with marked clubbing of the fingers and toes. There were a few signs of congestive heart failure. At the apical area a Grade 1 systolic murmur was heard. The second pulmonary sound was markedly accentuated.

X-Ray Examination.—The heart, especially in the left cavities, was enlarged (Fig. 1). In the frontal position the middle arch was slightly concave and the pulmonary circulation was approximately normal. In the left anterior oblique view the contour of the right ventricle was separated

Received for publication Oct. 12, 1959.

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Fig. 1.—X-ray films of the patient. Notice in the frontal view the absence of a prominent pulmonary artery in contrast to the good vascularity of the lung fields. The right anterior oblique view shows an enlarged left auricle. Both oblique views show a ventrally placed aorta (indicated by the arrow). Left ventricular enlargement is seen in the left anterior oblique view.

from the chest wall. Above this contour the ascending aorta was seen. The left ventricle was enlarged. In the right anterior oblique view the shadow of the right ventricle came in contact with the chest wall. There was no concavity of the middle arch; rather, this segment was convex and continuous with the lower convex contour of the right ventricle. The barium-filled esophagus was displaced backwardly, indicating left auricular enlargement.

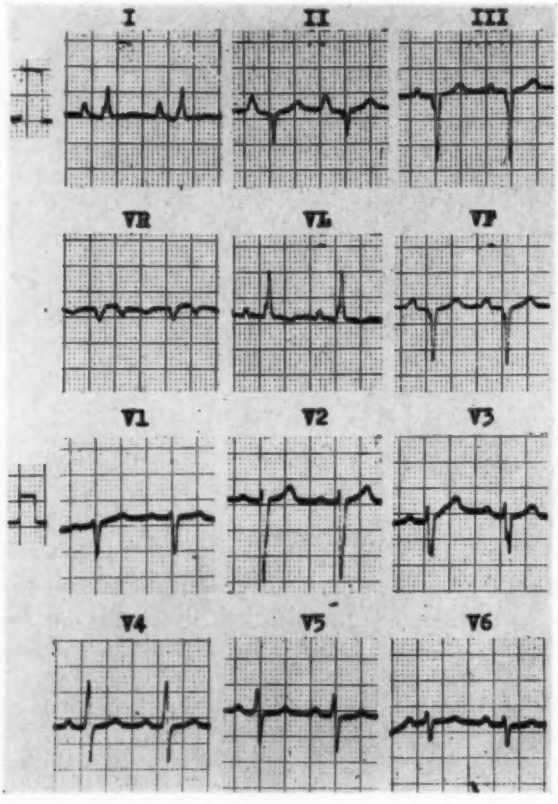


Fig. 2.—Electrocardiogram of the patient. Notice the tall peaked P waves in Leads I and II and the marked left axis deviation. The rS type of complex in all of the precordial leads is indicative of right ventricular enlargement. The flat T wave in Lead I and the negative T wave in Lead aVL suggest left ventricular enlargement.

Electrocardiogram.—The P wave was tall and pointed in Leads I and II. It measured 3 mm. and showed a slight notch in its descending portion. The axis of P (ÂP) was at +40°; ÂQRS was at −50°. The ascending portion of R in Leads I and VL showed slurring and a notch. There was absence of Q in the same leads. The S-T segment was straight, and the T wave was diphasic, of the minus-plus type in Leads I and VL. In Lead V_1 the ventricular complex was of the rS type, with a positive T wave; in Lead V_4 it changed to RS. A positive T wave was present in all precordial leads. The tracing was suggestive of enlargement of both auricles, left ventricular hypertrophy, incomplete left bundle branch block, and right ventricular hypertrophy (Fig. 2).

Course.—The patient was hospitalized in a poor condition. There was no time for specialized studies, and despite intensive treatment of the heart failure, he died on the third day.

Autopsy findings were limited to the heart (Fig. 3). Both ventricles were enlarged and hypertrophic. The aorta arose ventral to the pulmonary artery from both ventricles and was parallel to this vessel, which was narrow (Fig. 3,*A* and *B*). The right-sided ventricle proved to be the anatomic right ventricle, in view of the characteristics of the septum and the arrangement of the papillary muscles (Fig. 3,*C*). The communication between the auricle and the ventricle was

narrow and guarded by a tricuspid valve. The outflow chamber of this ventricle communicated with the outflow chamber of the opposite ventricle by a large ventricular septal defect which the aorta overrode (Fig. 3,*A* and *C*). This vessel was placed ventral to a muscular crescent-shaped structure which extended from near the tricuspid orifice in the lateral wall of the right ventricle to the anterior wall of the left ventricle, similarly to the crista supraventricularis (Fig. 3,*C*).

The left-sided ventricle had the anatomic characteristics of the left ventricle: two groups of papillary muscles, an anterior and a posterior group (Fig. 3,*A*). The upper two thirds of the septum had a smooth surface. From this ventricle, behind the structure referred to as being similar

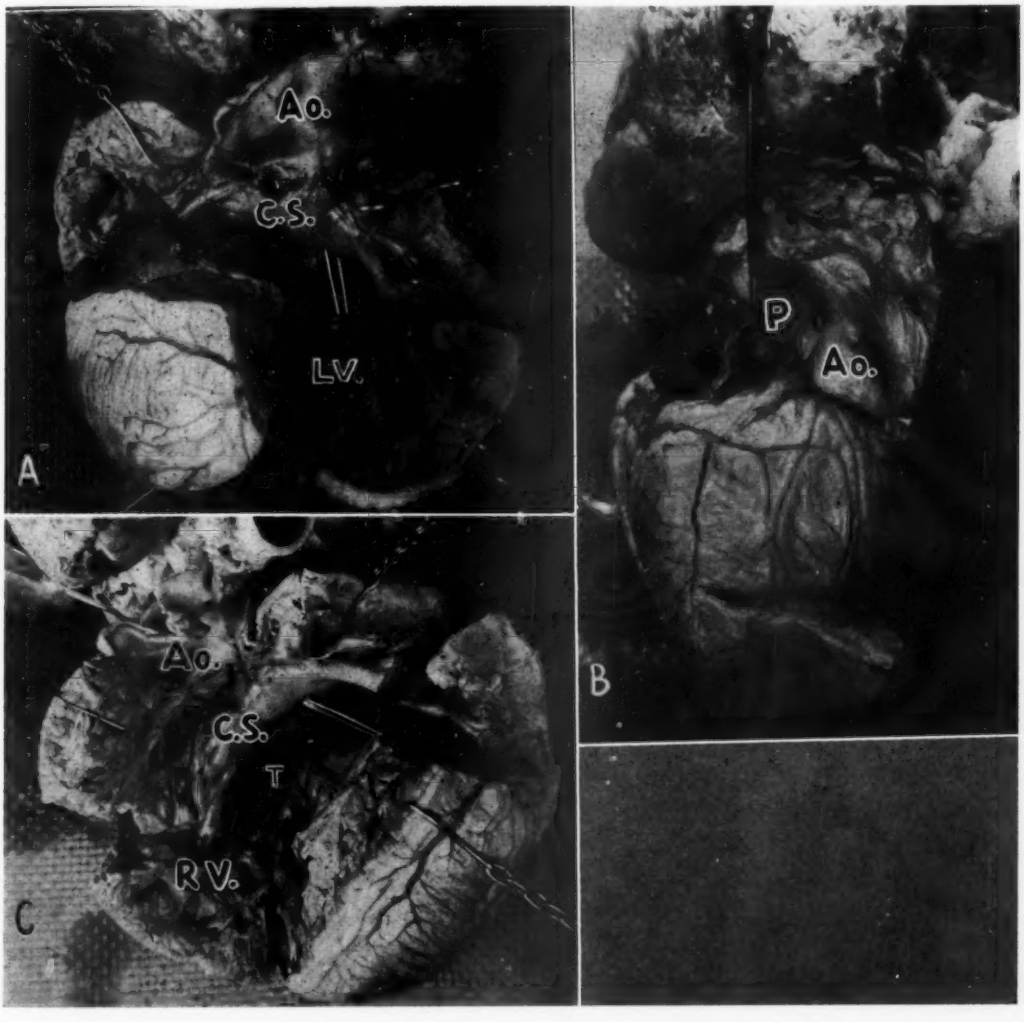


Fig. 3.—Biventricular transposed aorta and left ventricular stenotic pulmonary artery (transposition plus unequal partitioning at the expense of the pulmonary artery). *A*, Both ventricles are open in order to show the biventricular aorta (*Ao*) arising in front of the crista supraventricularis (*C.S.*) and overriding a ventricular septal defect. Behind the crista supraventricularis, arising from the left ventricle (*L. V.*), is the orifice of the pulmonary artery, indicated by the probe. Notice the marked hypertrophy of the left ventricle, which shows a characteristic trabecular aspect. *B*, Right lateral view of the heart and great vessels. The aorta (*Ao.*) is ventral with respect to the pulmonary artery (*P*) and it runs parallel to that vessel. The pulmonary artery is of narrow caliber and shows a probe introduced into the funnel-shaped valvular orifice. *C*, In this view the biventricular aorta is seen arising in front of the crista supraventricularis (*C.S.*), which extends from the free wall of the right ventricle (*R.V.*) in the vicinity of the tricuspid orifice (*T*) to the anterior wall of the left ventricle. The right ventricle shows characteristic trabeculations and a hypertrophic wall.

to a crista supraventricularis, arose the pulmonary artery with a narrow orifice, its sigmoid valve cusps fused into the shape of a funnel (Fig. 3,*A* and *B*). The inflow portion of the left ventricle exhibited a valve with two large cusps and a small cusp. Its relationship with the anterior and posterior papillary muscles indicated that it was a tricuspid mitral valve.

No sign of an interatrial septum was found. Although there was a single auricle, a normal relationship was maintained between the auricles and the ventricles. The right portion of the auricle exhibited the crista terminalis and connected with the two venae cavae and with the right ventricle through the tricuspid valve leaflets. On the other hand, the left auricular portion of the single auricle connected with the four pulmonary veins and with the left ventricle through the mitral leaflets.

The final anatomic diagnosis was: (1) transposition of the great vessels plus unequal partitioning at the expense of the pulmonary artery, (2) tricuspid stenosis, and (3) single auricle.

DISCUSSION

Anatomy and Embryology.—One of us (M.V.C.)[4] has pointed out that the truncoconal malformations are produced by the isolated or combined abnormal development of one of three elements: (1) conoventricular flange, (2) truncoconal septum, (3) primordia of the aortic and pulmonary sigmoid valve cusps.

On the basis of this theory,[4] fourteen different anatomic groups of truncoconal malformations were anticipated, some produced by a disorder in the development of an isolated embryonic structure, such as the abnormally early or late disappearance of the conoventricular flange which gives rise to isolated lateral positions. Others are the result of two disorders of development of a single embryonic component, as in the case of the straight development and abnormal position of the truncoconal ridges which unequally divide the truncus-conus at the expense of the pulmonary artery. This particular disorder gives rise to the anatomic picture of transposition of the great vessels plus unequal partitioning at the expense of the pulmonary artery. There are also groups of malformations produced by the abnormal development of two embryologic components, as in the case of late disappearance of the conoventricular flange and straight development of the truncoconal ridges. This complex disorder gives rise to lateral positions (dextropositions) plus transposition. Finally, some complex groups are the result of the abnormal development of two embryologic components, one of which has undergone a double developmental disorder. Such is the case when the conoventricular flange disappears late. Simultaneously, the truncoconal ridges develop in a straight fashion and are abnormally situated, thus dividing unequally the truncus-conus at the expense of the pulmonary artery. This would give rise to a lateral position (dextroposition) plus transposition with unequal partitioning at the expense of the pulmonary artery.

Table I gives a synoptic idea of the fourteen groups of truncoconal heart malformations and their relation with the developmental disorder which gives rise to them.

Some of the fourteen groups described were found to correspond to classic anatomic malformations, such as tetralogy of Fallot, Eisenmenger complex, etc. Others correspond to unusual malformations which, to our knowledge, have not been found and described before this theory was developed, such as the cases described by De la Cruz and associates[5] and Bret and associates,[1] in which the aorta and the pulmonary artery arise from the right ventricle, the former

vessel being located in front of the crista supraventricularis, running parallel and ventral to the narrow pulmonary artery which overrides a ventricular septal defect (lateral position plus transposition with unequal partitioning at the expense of the pulmonary artery).

Grosse-Brockhoff and Shaede[9] described a case in which the aorta was biventricular and overrode a ventricular septal defect in front of the crista supraventricularis, running ventral and parallel to a normal-sized pulmonary artery arising from the left ventricle (lateral position plus transposition).

The specimen described in this paper belongs to the type of malformation which was anticipated as belonging to Group 11, i.e., a transposition plus unequal partitioning at the expense of the pulmonary artery (Figs. 3 and 4,*B*). Its anatomic description was as follows: "The general anatomic characteristics for transposition plus unequal partitioning at the expense of the pulmonary artery are: A stenotic pulmonary artery emerges from the left ventricle and the aorta, of normal or increased caliber, overrides an interventricular communication. The ascending aorta lies ventral and parallel to the pulmonary trunk. It arises from both ventricles in front of the supraventricular ridge (crista supraventricularis)."[4]

This anatomic picture is explained on the basis of a double developmental disorder of the truncoconal ridges being present; that is, the ridges give rise to a straight septum and simultaneously divide unequally the truncus-conus at the expense of the pulmonary artery. If the truncoconal ridges develop in a straight fashion, without further disorder in their development, they would only originate a straight septum. This would cause the branches of the pulmonary artery (sixth aortic arch), related to the sinistrodorsal area of the cephalic end of the truncus, to communicate with the ventricle occupying the same spatial position in the caudal end of the conus, that is, the left ventricle. Simultaneously, the fourth aortic arch (horizontal portion of the aorta), which is in close relation with the dextroventral portion of the cephalic end of the truncus, would communicate with the dextroventral ventricle, that is, the right ventricle (Fig. 4,*A*). This, in turn, would cause the aorta to arise from the right ventricle in front of the crista supraventricularis and to run parallel and ventral to the pulmonary artery, arising from the left ventricle. This is none other than the anatomic picture of a classic complete transposition of the great vessels. If the ridges of the truncoconal septum lack the normal spiral rotation, a straight truncoconal septum will develop. If, in addition, the ridges of the truncoconal septum arise displaced backwardly toward the sinistrodorsal portion of the truncus-conus, the aorta will continue to occupy a ventral position, arising in front of the crista supraventricularis (straight truncoconal septum), but it will be a biventricular vessel overriding a ventricular septal defect because of the anomalous position of the truncoconal septum (Fig. 4,*B* and *C*). The ventricular septal defect is due, therefore, to the absence of alignment of the caudal end of the septum with the muscular portion of the ventricular septum (Fig. 4,*B* and *C*). On the other hand, the pulmonary artery will still arise from the left ventricle, and it will be a narrow vessel located behind the crista supraventricularis, which separates it from the aorta (Fig. 4,*B* and *C*). This anatomic picture is not that of a complete

TABLE I. CONGENITAL TRUNCOCONAL MALFORMATIONS

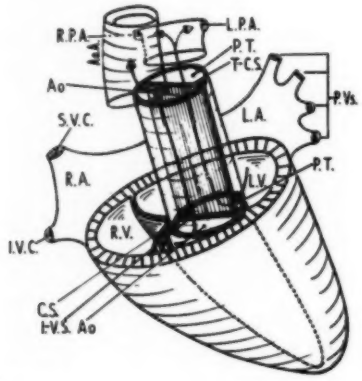
DIFFERENT GROUPS OF CONGENITAL TRUNCOCONAL MALFORMATIONS	NUMBER OF COMPONENTS AND EXTENT OF THE DISORDER INVOLVED	ABNORMAL DEVELOPMENT OF THE EMBRYOLOGIC COMPONENTS	TYPE OF CONGENITAL HEART DISEASE
1. Isolated lateral positions	Single component	Early or late disappearance of the conoventricular flange	Still not found* Eisenmenger**
2. Isolated common truncus		Absence of the truncoconal ridges	Common truncus
3. Isolated transposition		Straight development of the truncoconal ridges	Complete transposition of the great vessels
4. Isolated partial distortion		Incomplete rotation of the truncoconal ridges	Taussig-Bing[10]
5. Isolated unequal partitioning at the expense of the pulmonary artery		Unequal partition of the truncus-conus at the expense of the pulmonary artery	Tetralogy of Fallot
6. Isolated unequal partitioning at the expense of the aorta		Unequal partition of the truncus-conus at the expense of the aorta	Still not found

7. Lateral positions plus common truncus	Two components	Early or late disappearance of the conoventricular flange plus absence of truncoconal ridges	Varieties of common truncus[3]
8. Lateral positions plus transposition		Early or late disappearance of the conoventricular flange plus straight development of the truncoconal ridges	Case of Grosse-Brockhoff and Shaede[9]* Variety of Taussig-Bing[3]**
9. Lateral positions plus unequal partitioning at the expense of the pulmonary artery		Early or late disappearance of the conoventricular flange plus unequal partition of the truncus-conus at the expense of the pulmonary artery	Still not found* Variety of tetralogy of Fallot**
10. Lateral positions plus unequal partitioning at the expense of the aorta		Early or late disappearance of the conoventricular flange plus unequal partition of the truncus-conus at the expense of the aorta	Still not found* Variety of Eisenmenger complex**
11. Transposition plus unequal partitioning at the expense of the pulmonary artery	Double disorder of a single component	The truncoconal ridges develop in a straight fashion and divide unequally the truncus-conus at the expense of the pulmonary artery	Case discussed in this paper
12. Transposition plus unequal partitioning at the expense of the aorta		The truncoconal ridges develop in a straight fashion and divide unequally the truncus-conus at the expense of the aorta	Still not found
13. Lateral positions plus transposition with unequal partitioning at the expense of the pulmonary artery	Two components, one of which has a double disorder	Early or late disappearance of the conoventricular flange plus straight development of the truncoconal ridges which divide unequally the truncus-conus at the expense of the pulmonary artery	Still not found* Cases described by De la Cruz, Espino-Vela, and Fiamberti[5]** Cases described by Bret, et al.[1]**
14. Lateral positions plus transposition with unequal partitioning at the expense of the aorta		Early or late disappearance of the conoventricular flange plus straight development of the truncoconal ridges which divide unequally the truncus-conus at the expense of the aorta	Still not found* Still not found**

*Early disappearance of conoventricular flange.
**Late disappearance of conoventricular flange.

transposition of the great vessels (isolated transposition) (Fig. 3,*A*); instead, it shows the variant caused by the unequal partitioning of the truncus-conus at the expense of the pulmonary artery. Yet it maintains the fundamental features pertaining to the straight development of the truncoconal septum which give it the transposition component and produce this new variety of transposition of the great vessels, i.e., transposition plus unequal partitioning at the expense of the pulmonary artery (Figs. 3 and 4,*B*,*C*).

Our patient also had a single auricle and a tricuspid stenosis. It is evident, therefore, that truncoconal malformations may be found either in a "pure" form or associated with other cardiac malformations.[4]



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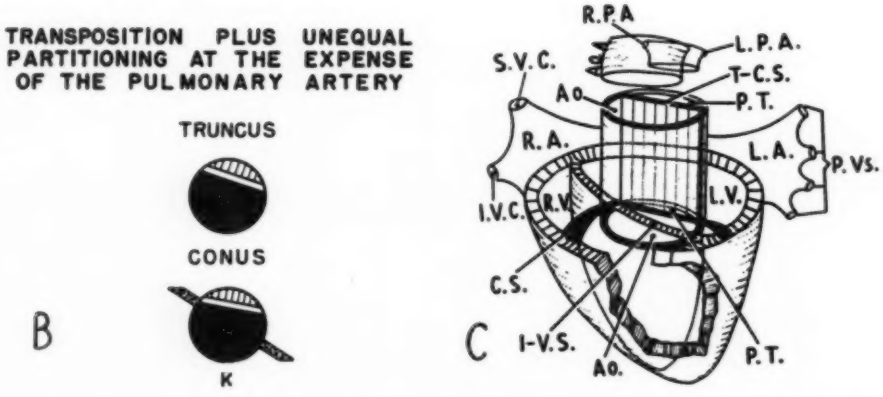

Fig. 4.—*A*, Schematic representation of classic transposition of the great vessels. *B*, Schematic representation of the transposition plus unequal partitioning at the expense of the pulmonary artery which was hypothetically predicted before the discovery of a postmortem case.[4] Diagrams of the positions of the great vessels at the cephalic end of the truncus and at the caudal end of the conus, as well as the relationship of the conal region of both vessels with the interventricular septum. Black area: aorta (ascending and conus). Striped area: pulmonary artery (trunk and conus). Dotted area: interventricular septum. *C*, Schematic representation of the actual case which exactly corresponded to the previously formulated prediction. Abbreviations in *A* and *C*: *Ao.*: Aorta. *Ao.A.*: Aortic arch. *C.S.*: Crista supraventricularis. *I.V.C.*: Inferior vena cava. *I-V.S.*: Interventricular septum. *L.A.*: Left atrium. *L.P.A.*: Left pulmonary artery. *L.V.*: Left ventricle. *P.T.*: Pulmonary trunk. *P.Vs.*: Pulmonary veins. *R.A.*: Right atrium. *R.P.A.*: Right pulmonary artery. *R.V.*: Right ventricle. *S.V.C.*: Superior vena cava. *T-C.S.*: Truncoconal septum.

Clinical Discussion.—Even though the diagnosis of this case was not made in vivo, some diagnostic suggestions might have been made in part. The most obvious one seems to be that of transposition of the great vessels. Especially reminiscent of this diagnosis is the radiologic aspect of the heart, which in the frontal view shows a concave middle segment. In the oblique views this concavity disappears and is replaced by the prominence of a vessel whose anterior contour is tangent to the anterior contour of the underlying ventricle (see arrows in Fig. 1). Likewise, the normal appearance of the pulmonary vascularity suggests transposition of the great vessels in view of the contrast of this aspect with the concavity of the middle segment. A right-to-left shunt was likewise obvious. Left-sided enlargement of the heart chambers is also apparent.

With regard to the last point, it is interesting to note that the great majority of varieties of transposition of the great vessels lead to right-sided enlargement of the heart cavities, because the right ventricle faces the aortic systemic resistances. Up to the present time, the only two known varieties of transposition which overload primarily the left cardiac chambers are transposition of the great vessels associated with tricuspid atresia and the type of transposition under discussion. In the former, left ventricular hypertrophy is evident in view of the presence of a single functioning ventricle, the left one. In the variety under discussion there is a biventricular aorta and a narrow pulmonary artery arising from the left ventricle. In other words, the left ventricle has to overcome two resistances, the aortic and the pulmonary (narrow pulmonary artery), whereas the right ventricle empties its contents only into the aorta. Furthermore, there was present in this specimen a tricuspid stenosis (Fig. 3) and a single auricle. Because of these, a large right-to-left shunt took place at the auricular level: hence, the large "left auricle" seen in the left oblique view of the x-ray study and the deep cyanosis of the patient.

Except in rare instances the life expectancy of patients with transposition of the great vessels of the ordinary type is short. When the transposition is complicated by pulmonary stenosis, life expectancy is not uncommonly greater.[5,6] Pulmonary stenosis seems to act as a protective mechanism against pulmonary flooding and very large volumetric overloading of all the cardiac chambers. Both of these conditions apparently were present in our patient, whose life was prolonged for an unusual length of time.

The diagnosis of this malformation might be entertained when the following several findings are present: clinically, early and deep cyanosis, yet with physical endurance not importantly decreased; radiologically, data compatible with the diagnosis of transposition of the great vessels, i.e., a relatively narrow pedicle and a concave middle segment, hilar vascularity of approximately normal size, and anterior aorta as visualized in the lateral views; electrocardiographically, a left ventricular hypertrophy, right ventricular hypertrophy, and biauricular hypertrophy.

Hypothetically, too, the use of simultaneous catheterization and angiocardiography should prove that there is an anterior overriding aorta. The pulmonary artery cannot be entered from the right chambers unless there is simultaneously a septal defect through which the catheter can be passed into the left

ventricle.[2] If the catheter is passed into the left cavities, and especially into the left ventricle, the injection of opaque substance should prove: (1) that the pulmonary artery fills from the left ventricle, and (2) that the aorta also fills partially from the left ventricle, i.e., it overrides the ventricular septum.

SUMMARY

A case of biventricular transposed aorta and a stenotic pulmonary artery arising from the left ventricle has been presented. The anatomic picture is a new variant of transposition of the great vessels. It illustrates a type of malformation anticipated in an embryologic theory recently developed.[4]

The authors wish to express their gratitude to Dr. M. Concepción Ruiz for permission to study the specimen herein described.

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Review

Total Anomalous Pulmonary Venous Connection

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Total anomalous pulmonary venous connection was first described in 1798,[1] but it was not until 1950[2] that the first case was reported in which the clinical diagnosis was made, and this was accomplished through the use of cardiac catheterization.

As previously used,[3] the term "total anomalous pulmonary venous connection" is a designation for a group of varied anatomic entities in which there is congenital abnormal connection of the entire pulmonary venous return. Some of the different types are characterized by normal drainage, either complete or partial, of the pulmonary venous return into the left atrium. Most commonly, however, when anomalous connection exists, all of the pulmonary venous return is by way of connection to the right atrium or one of its tributaries. Thus, this group includes not only total anomalous pulmonary venous connection but also total anomalous pulmonary venous drainage. It is this form of total anomalous pulmonary venous connection with which this presentation is concerned.

SCOPE OF PRESENT STUDY

Recent advances in cardiac surgery now make surgical correction of this anomaly possible. At the present time, we are aware of 24 patients† who were operated upon specifically for correction of total anomalous pulmonary venous connection.[2,4-13] Thus, the emphasis in this entity has changed rapidly from a description of the fundamental embryology, pathologic anatomy, and gross alterations in circulation to a better understanding of the varying hemodynamic features among patients with this anomaly and how best to correct the defect surgically. Most of the patients on whom hemodynamic data are available, however, belong to a selected group, namely, those who have survived beyond

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Received for publication Feb. 11, 1960.

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†Since the preparation of this manuscript, this figure has been increased to at least 46.

the usual age of death for patients with this anomaly. Therefore, such patients cannot be considered as representative of the complete clinicopathologic picture. An analysis of all reported cases, regardless of whether or not hemodynamic data exist, would give a broader view.

With this in mind, an attempt was made to collect all the available reports of cases of total anomalous pulmonary venous connection with total anomalous pulmonary venous drainage. A total of 188 such cases was obtained from the following sources: (1) reports of 176 cases in the literature (through May, 1956) proved by necropsy or operation, or both; and (2) a group of 12 cases not reported previously. Ten of the latter cases were from either the Mayo Clinic pathologic collection or the surgical records, whereas two represented living patients whose data were contributed for this analysis by Senning and associates.[11]

This review was done with several purposes in mind. One was to determine the relative incidence of total anomalous connection that occurs in the absence of other significant cardiac malformations, and of that form in which the venous malformation is associated with other serious cardiac malformations. The relative incidence of the various sites of anomalous pulmonary venous termination also was determined.

The clinical picture in total anomalous pulmonary venous connection with total anomalous drainage varies considerably from patient to patient. Extremes are the cyanotic newborn infant who dies in the first few weeks after birth and the noncyanotic adult with relatively little disability. Particular emphasis was placed on an attempt to explain the basis for this striking difference among patients. Our approach was stimulated by the suggestion of Burchell[14] that the size of the interatrial communication may influence the behavior of the circulation, and that the resistance to flow from the pulmonary circulation imparted by the anomalous pulmonary veins also might have an influence.

Since the resistance to flow through a vessel is influenced not only by the diameter of the vessel but also by its length, it became apparent that the malformation under consideration could be classified according to the length of the anomalous pulmonary veins into three categories, namely, "short," "intermediate," and "long" routes. Short routes included anomalous pulmonary venous connections into or close to the right atrium, as into the superior vena cava or the coronary sinus. Connection into the left innominate vein represented an intermediate route. Termination into the inferior vena cava, part of the portal venous system, or a ductus venosus represented a long route.

In this malformation, the common receiving chamber is the right atrium. From it, blood is distributed to the lesser circulation through the tricuspid orifice and to the greater circulation through the interatrial communication. The relative volumes that flow in each direction depend on the resistance to flow in each route. The size of the interatrial communication influences the flow into the greater circulation. All other conditions being equal, the wider the interatrial communication, the less is the resistance to flow through it, and the greater is the volume of flow.

The factor that principally influences the volume of flow through the tricuspid valve is the distensibility of the right ventricle. The thicker the wall of

this chamber, the greater is the resistance to flow through the tricuspid valve; all other conditions being equal, the thicker the right ventricle, the less is the flow through the tricuspid valve.

Thus, in this malformation, the distribution of right atrial blood depends on the size of the interatrial communication and the thickness of the right ventricular wall; the latter depends to a major degree on the right ventricular and pulmonary arterial pressures. It is appropriate to postulate that the pulmonary arterial pressure in total anomalous pulmonary venous connection depends to a considerable extent on the pulmonary venous pressure; any increase in the latter would be accompanied by an increase in pulmonary arterial pressure.

GENERAL CONSIDERATIONS

Of these 188 patients with total anomalous pulmonary venous connection associated with total anomalous drainage, 66 patients[1,9,15-60] had major associated cardiac malformations, including cor biloculare, cor triloculare biatriatum, persistent truncus arteriosus, complete transposition of the great vessels, pulmonary stenosis or atresia, coarctation of the aorta, anomalous connections of the systemic veins, or complex intracardiac malformations associated with agenesis of the spleen, as described by Ivemark[55] and others.[30,50,51,53,54] In three cases,[61] data as to the presence or absence of associated defects were not given. The remaining 119 cases, all classified as not having associated major cardiac malformation, included six instances[61,62,63 (Case 3)] in which data were not given as to the exact site of the anomalous pulmonary venous connection. Thus, 113 cases without major associated cardiac malformation could be analyzed as to the site of connection. In some of these latter cases, an "atrial septal defect" was listed as the type of interatrial communication present, a condition that for the purposes of this paper was not considered to be an associated major cardiac malformation.

These 113 cases without major associated anomalies and the 66 with associated major cardiac malformations make a total of 179 cases, which have been analyzed principally as to the site of connection of the anomalous pulmonary veins. Table I and the remainder of this section concern these 179 cases of total anomalous venous connection. The anomaly was more frequent in males than in females; of the 131 patients for whom the sex was given, 80 were male and 51 were female.

In general, the pulmonary veins converged to join a single anatomic location in the systemic venous system. Two anatomic types of junction were present, one in which the pulmonary veins converged to form a single trunk before connecting anomalously, and one in which two or more pulmonary veins connected to the single structure receiving the veins. When the site of connection was more peripheral than the right atrium or the superior vena cava, the connection was always a single trunk; among the cases with connection to the right atrium, the superior vena cava or the coronary sinus, either a single trunk or multiple pulmonary venous connections were found. The literature contained reports of 15 exceptions to this basic pattern of anomalous connection, in that the pulmonary veins entered multiple systemic venous structures instead of a single anatomic location. These cases will be discussed later.

The most common site of entry in the entire group was by way of an anomalous vertical vein joining the left innominate vein. The next two most frequent sites of connection were the right atrium and the right superior vena cava. The group with associated major cardiac malformations did not contain any cases in which the anomalous connection was with the coronary sinus, but 18 such cases were present among the group without malformations, comprising the second most common connection in this subgroup. Less common connections into the systemic venous system were with the portal vein, ductus venosus, true persistent left superior vena cava, inferior vena cava, azygos vein, right innominate vein, and hepatic vein. When the connection was to the portal vein, the

TABLE I. DATA IN 179 CASES OF TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION

	ASSOCIATED MAJOR CARDIAC MALFORMATION		
	YES*	NO	TOTAL
Male	31	49	80
Female	23	28	51
Sex not given	12	36	48
Total	66	113	179
Site of connection			
Left innominate vein	10 (18, 25, 28, 29, 47, 50, 54, 55 [Cases 8 and 15], 58)	41	51
Right atrium	13 (19, 20, 22, 24, 30, 33 [two cases], 9, 48, 56 [two cases], 37, 38)	17	30
Coronary sinus	0	18	18
Right superior vena cava	14 (21, 30, 31, 35, 40, 42, 51 [Case 1], 55 [Cases 1, 13, 17], 23, 36, 53, 54)	12	26
Portal vein	10 (27, 29, 34, 39, 44, 45, 49, 55 [Case 6], 58, 59)	7	17
Ductus venosus	2 (16, 43)	4	6
Left superior vena cava	5 (1, 17, 41, 42 [Case 1], 9)	0	5
Right innominate vein	2 (26, 55 [Case 11])	0	2
Inferior vena cava	2 (9, 32)	2	4
Azygos vein	3 (55 [Case 12], 52 [Case 5], 57)	0	3
Hepatic vein	0	1	1
Multiple sites†	5 (15, 51 [Case 2], 53, 54, 9 [two cases])	8	13
Exact site uncertain	0	3	3
Total	66	113	179

*Numbers in parentheses are reference numbers.
†Two additional cases of Soulié,[61] with insufficient data for classification.

anomalous vein reached the abdomen through the esophageal hiatus. When the connection was to the ductus venosus, the vein sometimes accompanied the esophagus,[64] but in other instances it entered the abdomen through the orifice for the inferior vena cava.[43,65] All of the cases in which the connection was to a true persistent left superior vena cava were in the subgroup with associated major cardiac malformations.

Exceptions to Basic Pattern.—As already noted, there were 15 exceptions to the basic pattern of connection, in that multiple locations of anomalous pulmonary venous connection were present. Five of these patients had associated major cardiac malformations and eight did not. In the remaining two patients,[61] the information was not sufficient to allow the state of the heart to be determined.

Among the five cases in which multiple sites of connection were associated with major cardiac malformations, Case 2 of Boggs and Reed[51] had three sites of connection, namely, the left superior pulmonary vein connecting with the left subclavian vein, the right superior pulmonary vein joining the right atrium, and the inferior pulmonary veins forming a common trunk connecting with the inferior vena cava. In Ramsbotham's case,[15] which was the first divergent type of connection described in the literature, the left pulmonary veins formed a common trunk joining the left subclavian vein, whereas the right pulmonary veins connected with the portal vein by a common trunk. In two cases, one described by Baumann,[53] (Case 1) which was also reported by Willi and Gasser,[54] (Case 6) and the other by Gott and associates,[9] the pulmonary veins from each lung formed separate trunks, the right trunk connecting with the right superior vena cava, and the left common trunk connecting with a true persistent left superior vena cava. The fifth case, also reported by Gott and associates, had a common trunk receiving all of the pulmonary veins. This common trunk entered the abdomen and then divided into multiple small branches that joined the pancreatic and mesenteric veins.

The eight cases with multiple anomalous connections but without associated major cardiac malformations included two cases with contiguous sites of connection, reported respectively by Muller[4] and by Sepulveda and associates.[8] In Muller's case, the right superior pulmonary vein connected with the right superior vena cava, whereas the remaining pulmonary veins formed a trunk that directly entered the right atrium. In the latter case, the right pulmonary veins formed a trunk that connected with the right superior vena cava, whereas the left pulmonary veins formed a trunk that directly entered the right atrium. In the remaining six cases of this subgroup, the connections were anatomically distant. Bochdalek[66] reported a case in which the right pulmonary veins connected by a single trunk with the azygos vein at its junction with the superior vena cava, whereas the left pulmonary veins formed a trunk that entered the abdomen to connect with the portal vein. Three other cases were similar, in that part of the connection was to the right atrium itself or the superior vena cava, and the other part was to the left innominate vein. In Rebensburg's case,[67] the pulmonary vein from the right upper lobe connected with the right atrium, and the rest of the pulmonary veins formed a trunk that connected with the left innominate vein. Thérémin[68] described a situation in which all of the right

pulmonary veins formed a trunk that directly entered the right atrium, whereas a trunk formed by the left pulmonary veins entered the left innominate vein. In Winter's case,[69] the veins from the right middle and right upper lobes connected with the superior vena cava, and those from the left upper lobe and both lower lobes formed a trunk connecting with the left innominate vein. The remaining two cases, reported by Gott and associates, were different, in that one had connections with the coronary sinus and the left innominate vein, whereas the other showed connections with the inferior vena cava and the left innominate vein.

The remaining two of the 15 cases in this group also deserve mention because of their multiple sites of pulmonary venous connection.[61] These two cases otherwise are not included in the over-all analysis in this paper because of lack of certain information. In one case, three pulmonary veins connected with the right atrium and the fourth vein connected with the left innominate vein; in the other case, three pulmonary veins entered the coronary sinus and the fourth vein connected with the left subclavian vein.

TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION WITHOUT ASSOCIATED MAJOR CARDIAC MALFORMATIONS

The 113 cases of total anomalous pulmonary venous connection without associated major cardiac malformations included 24 cases in which data were not available as to the patient's age or the type of interatrial communication present.[4-6,9,70] An additional eight cases had multiple sites of connection of the anomalous veins, a feature that was thought to complicate any analysis.[4,8,9,68,71] These latter cases already have been discussed. Thus, from the entire series, we were able to collect 81 cases in which the data were adequate for our analysis.

Anatomic Considerations.—The right side of the heart was moderately to greatly dilated and hypertrophied, whereas the left atrium and ventricle were small. In most instances, this discrepancy was thought to be absolute as well as relative; however, in a few infants, the left ventricle was described as normal in size for the age.

An interatrial communication was present in all cases, with the term "patent foramen ovale" predominating over "atrial septal defect." This group did not contain any cases in which the atrial septal defect was of the type associated with a persistent common atrioventricular canal.

When the site of anomalous connection was at a distance from the right atrium, the pulmonary veins converged to join a systemic vein at a single receiving site. Most commonly, the communication was by means of a single channel emerging from a point of convergence of the pulmonary veins from both lungs. The area of convergence sometimes was described as being dilated into a chamber-like organ, but this finding was not consistent. The anomalous convergence of the pulmonary veins lay posterior to the heart and the pericardium, either behind the left atrium or occasionally in the hilar region of one lung, with the veins from the opposite lung crossing the midline to join it.

As already noted, the most common site of connection with the systemic

venous circulation was by way of an anomalous vertical vein to the left innominate vein (Table I). This type of communication has been described frequently as a persistent left superior vena cava, but it has no connection with the heart and so cannot logically be called such a vessel. In order of frequency, the remaining sites of entry were the coronary sinus, right atrium, superior vena cava, portal vein, ductus venosus, inferior vena cava, and hepatic vein.

When the veins directly joined the superior vena cava or the right atrium, they often did so as separate channels instead of forming a common trunk.

An important surgical anatomic feature of total anomalous pulmonary venous connection without major associated cardiac malformation has been pointed out by Keith and associates.[7] In 10 of their 13 proved cases, they obtained measurements of both the anomalous vein and the "waist," or base, of the left auricular appendage; in seven of these 10 cases, the diameter of the waist was smaller than that of the anomalous pulmonary vein. Gott and associates[9] found a similar situation in their cases.

Relationship of Longevity to Type of Interatrial Communication and Site of Anomalous Connection.—The 81 cases of total anomalous pulmonary venous connection having a single receiving vessel or chamber and not associated with major cardiac malformations were analyzed as to longevity and the occurrence of cyanosis. These features were evaluated in relationship to the site of anomalous connection and the type of interatrial communication. Although the size of the interatrial communications usually was not given in exact figures, some general conclusions appear warranted.

For our purposes, all patients listed in the publications as having an "atrial septal defect" were considered to have larger interatrial communications than did those listed as having a "patent foramen ovale."

As noted previously, the resistance to pulmonary venous return depends not only on the length of the anomalous pathway that it must traverse but also on the diameter throughout the length of the veins concerned. Because the latter measurement was not obtainable, we are considering for the purposes of this analysis that anatomically longer routes of communication produce a greater resistance to pulmonary venous flow than do shorter routes.

Several patients with total anomalous pulmonary venous connection without associated major cardiac defects have lived for many years, but these patients cannot be included in the analysis because one or more of the variables necessary for comparison are unknown.[4 (Case 2), 8 (Case 5), 9 (Surgical Case 1)] An increasing number of cases are being reported in which the clinical diagnosis of total anomalous pulmonary venous connection appears to be valid. Not being proved, these cases cannot be included, and thus the number of older patients in this study is small. Despite these objections, it was thought that the over-all trends of the effects of the anatomic variables in the anomaly might help in an understanding of the underlying hemodynamic problems.

Of these 81 patients, 60 (74 per cent) were dead by 1 year of age; the majority of these died at the age of 6 months or earlier (Table II). Of the remaining 21 patients, 10 died between the ages of 1 and 5 years. Of the 11 who survived beyond 5 years of age, seven lived to the age of 14 years or more.

TABLE II. AGE AT DEATH OR OPERATION, AND INCIDENCE OF CYANOSIS IN 81 CASES OF SINGLE SITE OF TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION WITHOUT MAJOR ASSOCIATED CARDIAC MALFORMATION

GROUP	SITE OF CONNECTION	ATRIAL DEFECT*	NUMBER OF CASES (WITH REFERENCES IN PARENTHESES)	AGE		CYANOSIS					
				RANGE	AT DEATH OR OPERATION	AT BIRTH	6 MO. OR BEFORE	AFTER 6 MO.	TOTAL WITH CYANOSIS	NO CYANOSIS	NO DATA
IA (long route)	Ductus venosus	PFO	4 (64, 65 [Case 1], 72 [Case 3], 73)	—	Dead: 9, 15, 17 days, and 4 wk.	2	2	0	4	0	0
		ASD	None	—	—	—	—	—	—	—	—
	Portal vein	PFO	4 (74-77)	—	Dead: 45 hr., 15, 18 days, and 10 wk.	1	1	0	2	0	2
		ASD	2 (7, 78 [Case 13])	—	Dead: 21 days, 3 mo.	0	1	0	1	0	1
	Inferior vena cava in abdomen and hepatic vein	PFO	1 (63 [Case 23])	—	Dead: 2 mo.	0	1	0	1	0	0
		ASD	1 (79 [Case 23])	—	Dead: 2 mo. (hepatic vein)	0	1	0	1	0	0
IB (intermediate	Left innominate vein	PFO	22 (80-84 [Case 3], 85, 86 [Case 2], 87, 88 [Case 33], 2, 79 [Case 2†], 72 [Cases 1 and 2], 6 [Case 3], 89 [Case 1], 7 [Cases 1, 9, 10], 56 [II, Case 1], 10, 90, 91 [Case 2‡])	8 days-6 yr.	(6½ yr.‡); 13 dead at 6 mo.; 16 at 1 yr.; others at 16 mo., 2 yr.,‡ 3½ yr., 4 yr., 6 yr.	3	10	6	19	2	1
		ASD	10 (7, 92 [Cases 4, 5, 6, 7, 11], [2 cases], 93)	18 days-14 yr.	3 dead at 6 mo.; 6 at 1 yr.; others at 3½ yr., 7 yr.; 2 alive at 9 yr.,† 14 yr.†	0	3	6	9	0	1
Total, IA and IB			44		28 dead at 6 mo.; 34 at 1 yr.	6	19	12	37	2	5

II (short route)	Right atrium	PFO	7 (86, 94-96 [Case 1], 7, 97, 98 [Case 3])	25 days-9 mo.	5 dead by 6 mo.; others at 8 and 9 mo.	3	4	0	7	0	0
		ASD	7 (10, 99-101 [Cases 1† and 3†], 102,† 103‡)	3 mo.-27 yr.	2 dead at 3 and 5 mo.; others at 8½, 19, 23, 25, 27 yr.§	0	1	3	4	0	3
	Superior vena cava	PFO	7 (21, 104, 105 [Case 2], 2 [Case 1‡], 106 [Case 3], 7 [Case 2], 63 [Case 1])	7 days-4 yr.	6 dead by 4 mo.; others at 4 yr.	3	2	0	5	0	2
		ASD	3 (107-109)	8 wk.-31 yr.	2 dead at 8 and 11 wk.; other at 31 yr.	1	1	1	3	0	0
	Coronary sinus	PFO	10 (110-112 [Cases 1 and 2], 105, 113 [Case 1], 88 [Case 32], 114, 115	10 wk.-39 yr.	6 dead by 6 mo.; others at 8 mo., 19 mo., 2 yr., 39 yr.	1	4	3	8	1	1
		ASD	3 (7 [Case 12], 56, 116 [II, Case 2])		Dead at 7 mo.; 1 yr., 4 yr.§	0	0	2	2	0	1
	Total		37		21 dead at 6 mo.; 26 at 1 yr.	8	12	9	29	1	7
Grand total			81		47 dead at 6 mo.; 60 at 1 yr.	14	31	21	66	3	12

*PFO: Patent foramen ovale. ASD: Atrial septal defect.
†Operated upon and survived (five patients).
‡Operated upon, with surgical death (four patients).
§Patent ductus arteriosus.

The cases were subdivided into the following two major groups and six subgroups, depending on the presence of an atrial septal defect as opposed to a patent foramen ovale, and on the presence of long, intermediate, or short routes of anomalous pulmonary venous connections:

I. Anomalous connection of the pulmonary veins away from the right atrium

A. Connection at a distance from the right atrium (long route)

1. With patent foramen ovale
2. With atrial septal defect

B. Connection to the left innominate vein (intermediate route)

1. With patent foramen ovale
2. With atrial septal defect

II. Anomalous connection of the pulmonary veins contiguous to or directly into the right atrium (short route)

1. With patent foramen ovale
2. With atrial septal defect

From an over-all consideration of the problem of total anomalous pulmonary venous connection, it perhaps would be more sound anatomically to have three main groups based on the variables just listed. When survival was analyzed, however, it became apparent that the patients with venous connection to the left innominate vein behaved as an intermediate group. Thus, we have listed them as a subgroup of Group I, and these cases will be discussed in relationship to the trends seen in the two major groups.

Only one patient in the group with anomalous connection by a long route survived to adolescence. This patient[11(Case 2)] was 14 years of age at the time of surgical intervention, which disclosed an atrial septal defect.

In sharp contrast, six patients in the subgroup of 37 with a short connection to the systemic venous system lived to adolescence or adulthood; their respective ages were 19, 23, 25, 27, 31, and 39 years. Each of these patients was designated as having an atrial septal defect except the 39-year-old patient, in whom a patent foramen ovale was known to be about 2 cm. in diameter.

A contrast was noted in each of the subgroups with respect to the presence of a patent foramen ovale or an atrial septal defect. The patients having a long or intermediate anomalous connection of the pulmonary veins and a patent foramen ovale tended to die earlier than did the patients having a long or intermediate anomalous connection and an atrial septal defect.

Of the 24 patients with the short type of connection and a patent foramen ovale, 17 were dead by 6 months of age, and the remainder were dead by 4 years of age, with but one exception. The exception was a 39-year-old man with a connection to the coronary sinus and a patent foramen ovale; he represents one of the new cases reported in this paper. Although this patient had an anatomically valve-competent patent foramen ovale, the channel was 2 cm. in diameter.

In contrast to these patients were those with a short connection and an atrial septal defect. Four of these 13 patients were dead by 6 months. Three died at the ages of 7 months, 1 year, and 4 years, and the remaining six lived to 14 years of age or more, as already noted. Further analysis indicates the distinct

difference between the two anatomic extremes of patients with total anomalous pulmonary venous connection without associated major cardiac malformations, namely, those with the shortest communication and an atrial septal defect, and those with the longest communication and a patent foramen ovale. The first of these two categories included all but one of the seven patients who survived for 14 years or more. In sharp contrast, all nine patients in the second category had died by the age of 10 weeks.

As indicated previously, the patients whose connection is to the left innominate vein are anatomically an intermediate group between the other two extremes. Of the 22 patients with such a connection and a patent foramen ovale, 13 were dead at 6 months of age, and two survived to the ages of 4 and 6 years. When this type of anomalous connection was associated with an atrial septal defect, three of 10 patients were dead before the age of 6 months, three died between 6 months and 1 year of age, one died at 3½ years and one at 7 years of age. The remaining two patients survived operation at 9 and 14 years of age, respectively.

Thus, any combination of longer routes of anomalous connection and a patent foramen ovale severely limits the survival of patients with total anomalous pulmonary venous connection, and only patients with the most favorable anatomic features, namely, a short route of anomalous connection and a large interatrial communication, are among those with long survival times.

Patients with multiple sites of entry cannot be considered in the foregoing categories, but it is of interest to note that three patients with connections close to the right atrium and with an atrial septal defect lived to the ages of 16, 25, and 37 years, whereas two patients with a longer type of connection and a patent foramen ovale died at the ages of 4 days and 3 months.

Cyanosis.—The presence of cyanosis in patients with this anomaly generally has been accepted as a late or terminal event, but it has been pointed out that the anomaly should be classified in the group of lesions associated with cyanosis.[9,52] The general statement can be made that, since all the blood reaching the peripheral vascular system must be mixed with systemic venous and pulmonary venous blood, the degree of oxygen saturation of peripheral arterial blood depends in part on the amount of pulmonary flow relative to the amount of systemic flow.[102] Many of these patients, especially those in the older age groups, have not had cyanosis, but data obtained at cardiac catheterization have demonstrated a decrease in peripheral arterial oxygen saturation in most cases.[117]

Data concerning cyanosis were recorded in 69 of these 81 cases (Table II). Cyanosis never had been observed in three patients, whose ages were 4 months, 16 months, and 39 years, respectively. Fourteen patients had cyanosis at birth; five of these died in the first month of life, nine lived into the second month, six lived into the third month, and two lived to the ages of 6 and 8 months, respectively. In 31 additional patients, cyanosis was observed before the age of 6 months but not at birth; this is designated as "delayed cyanosis." Cyanosis was described variously as persistent, present on effort, or occurring in attacks. It was a terminal event in many instances. Of the 31 patients who had delayed cyanosis, 26 were dead by the age of 6 months. In the other five patients, cya-

nosis had been present for 6 months in a patient living to 8 months, and for 8 years in a patient operated on at 8½ years of age.

In the remaining 21 of the 69 cases, cyanosis developed after the age of 6 months, and this is termed "late" in onset. It was a terminal event in seven of these patients. Its exact duration was unknown in eight patients, but in six others, aged 8 and 19 months and 2, 4, 9, and 14 years, respectively, cyanosis had been present for 1½ months to 13 years.[2] (Case 3), 11 (two cases), 88 (Cases 32 and 33), 114

Thus, cyanosis varies greatly among patients with total anomalous pulmonary venous connection. In general, patients who are cyanotic at birth die early, whereas those who have late or delayed cyanosis survive longer. None of the patients who were cyanotic at birth lived beyond 8 months of age. Of six patients who lived to 14 years of age or beyond, five were not cyanotic at birth. A 14-year-old living patient has been cyanotic since the age of 1 year.[11] A 19-year-old patient was cyanotic for only 2 weeks before death.[99] Two other patients, aged 23 and 25 years, respectively, were not cyanotic in early childhood but had been cyanotic for a number of years before observation.[10] (Case 1), 12 A 39-year-old man never had been cyanotic.[115] The sixth patient, a Negro woman who was 31 years old at the time of death, had been cyanotic for at least 6 years before death, but the age at the onset of cyanosis was unknown.[109]

A difference was noted in the time of onset of cyanosis between patients with short routes of venous connection and those with longer routes. This difference is emphasized by a separate consideration of the patients with long routes and those with intermediate routes. Of 21 patients with the short route and a patent foramen ovale, 85 per cent were cyanotic at birth or by the age of 6 months, whereas only 33 per cent of nine patients with a short route and an atrial septal defect were cyanotic within this period. Among those patients with the intermediate route, connecting to the innominate vein, 68 per cent of 19 patients having a patent foramen ovale were cyanotic at birth or before the age of 6 months, whereas only 33 per cent of those who had an atrial septal defect were cyanotic within this period. In definite contrast, all nine cyanotic patients with a long route of connection were cyanotic at birth or before 6 months of age, regardless of whether they had an atrial septal defect or a patent foramen ovale.

Thus, cyanosis tends to be earlier in onset when the total anomalous pulmonary venous connection is associated with longer routes of connection and smaller interatrial communications.

CLINICAL CONSIDERATIONS IN DIAGNOSIS

Although the clinical features of total anomalous pulmonary venous connection frequently vary from patient to patient, the patients tend to fall into two groups, depending on the state of cardiac compensation. In either group, cyanosis may be present or absent. In the first group, cardiac decompensation is an early feature. When the patient is cyanotic, the rapidly enlarging heart brings into the differential diagnosis conditions such as complete transposition

of the great vessels, persistent truncus arteriosus, and other forms of cyanotic congenital heart disease. The second group includes patients who have only minor outward evidence of cardiac disability. These patients survive infancy, and some attain adulthood. Although cyanosis is more common in patients who have cardiac decompensation early in life, patients in this second group also may exhibit cyanosis. When cyanosis is absent, such patients may be confused with those having atrial septal defects. Those who survive infancy and are cyanotic may be confused with patients having various types of septal defects associated with pulmonary hypertension and a right-to-left shunt.

A murmur is present in the majority of patients who have this anomaly, although the murmurs show nothing characteristic. The murmurs usually are systolic and are heard over the left sternal border in the second or third intercostal space. The pulmonary second sound often is accentuated. Both these findings probably reflect high pulmonary flow or pulmonary hypertension, or both. Keith and co-workers[7] pointed out that anomalous connection into the left innominate vein may be associated with a soft systolic and diastolic murmur heard over this same region, although it is not consistently present and may be inconstant in the same patient. It is softer than the usual murmur caused by a patent ductus arteriosus.

The electrocardiogram reveals evidence of right ventricular hypertrophy or the so-called right ventricular overload pattern, with complete or partial right bundle branch block.

When the anomalous pulmonary vein terminates in the left innominate vein, the roentgenographic picture may show the figure-of-eight pattern described by Snellen and Albers.[5] Usually, this appearance is characteristic of total anomalous pulmonary venous connection, but, as pointed out by Sepulveda and associates in a proved case,[8 (Case 3)] connection of the left pulmonary veins solely to the left innominate vein may produce an identical picture. Bruwer[118] noted that other conditions can produce the same roentgenographic pattern. The thoracic roentgenogram in these cases generally shows an enlarged heart and increased pulmonary arterial vascular markings, both of which features are common to many other malformations associated with high pulmonary flows.

The diagnosis of total anomalous pulmonary venous connection is not easy but, as pointed out by DuShane,[119] its presence can be suspected from careful evaluation of all the afore-mentioned factors. Gardner and Oram[6] noted that difficulty in feeding accompanied by attacks of cyanosis may suggest an anomalous connection below the diaphragm. However, angiocardiography or cardiac catheterization, or both, are ultimately necessary to furnish the necessary data for definitive diagnosis.

COMMENT

Pathophysiologic Considerations.—The clinical picture of this anomaly, in conjunction with the type of connection of the anomalous veins and the type of interatrial communication present, suggests a pathophysiologic classification for these patients. As already noted, the patients who live longest tend to have the shortest communication between the pulmonary venous bed and the heart

and also to have the largest interatrial communications. Those who die at the youngest age have the longest route of pulmonary venous communication and the smallest interatrial communications. Patients with intermediate anatomic variations show an intermediate pattern of survival.

Thus, it appears reasonable to suggest the following four pathophysiologic patterns:

I. Patients with high resistance to flow through a long or a narrow or a long and narrow pulmonary venous route

A. With patent foramen ovale (small interatrial communication)

B. With atrial septal defect (large interatrial communication)

II. Patients with low resistance to flow through a short or a wide or a short and wide pulmonary venous return route

A. With patent foramen ovale (small interatrial communication)

B. With atrial septal defect (large interatrial communication)

The physiologic data available in 14 proved cases reported in the literature and in four of our own cases showed that severe degrees of pulmonary hypertension were associated with a patent foramen ovale and with death at an early age, and peripheral arterial desaturation was pronounced.

The following discussion of possible underlying hemodynamic phenomena is based on the preceding pathologic and physiologic findings.[22] The resistance along a tube is inversely proportional to the fourth power of its radius and directly proportional to its length. Thus, both of these attributes, either singly or in combination, considerably affect hemodynamics.

The resistance of flow from the right atrium into the systemic circulation depends on the size of the interatrial defect. If the communication is small, the resistance to outflow from the pulmonary circuit is greater, and pressure in the right atrium tends to be greater in order to maintain adequate systemic flow. This reasoning is borne out by the hemodynamic findings in patients with a patent foramen ovale and total anomalous pulmonary venous connection.

Accordingly, the following hemodynamic changes could be expected in the afore-mentioned four categories: *High resistance with patent foramen ovale:* Total pulmonary resistance is high, associated with pulmonary hypertension. Total pulmonary flow tends to be low, with an inclination toward severe cyanosis. There is also resistance to flow out of the entire pulmonary circuit because of the small interatrial communication, which further adds to the load on the right side of the heart and the *vis a fronte* of the pulmonary venous return. Early cardiac decompensation and death are to be expected in patients of this group. *High resistance with atrial septal defect*: The increased resistance to pulmonary outflow again decreases pulmonary flow. However, the flow into the left atrium is not impeded, as it is in the first instance, and the total resistance to pulmonary outflow is decreased. Also, the right side of the heart is not forced to handle the overloading problem to the same degree. The patients of this group tend to live longer than do those in the first group, with cardiac decompensation appearing later. *Low resistance with patent foramen ovale*: Pulmonary venous resistance is increased in relationship to the size of the interatrial septal defect, and the entire

load on the right side of the heart depends on the ability for outflow from the pulmonary circuit to occur. With small interatrial defects in patients of this group, early cardiac decompensation and death may be expected. *Low resistance with atrial septal defect*: This type of defect offers less resistance to flow at any point than do all of the previous lesions. The large pulmonary flow that is possible and usually present ensures against the tendency for peripheral arterial oxygen desaturation. Thus, the patients of this group do well for many years, until the overload on the right side of the heart, as in the case of an isolated atrial septal defect, becomes complicated by increased pulmonary vascular resistance, pulmonary hypertension, and cardiac decompensation.

Patent Ductus Arteriosus.—In this particular anomaly, a left-to-right shunt means a further load on a greatly overloaded pulmonary bed and a need for even a greater flow across the interatrial communication in order to supply the peripheral tissues with adequate circulation. Such further increased pulmonary flow could accentuate the development of secondary pulmonary changes, with curtailment of pulmonary flow for adequate oxygenation of the blood reaching the periphery. If, on the other hand, severe pulmonary hypertension already was present at an early age, the flow across such a patent ductus would be from right to left. Such a situation tends to perpetuate the decreased pulmonary flow present in the face of such pulmonary resistance, and the shunt of desaturated blood away from the lungs could only augment inadequate oxygenation. In time, the patient with the first type of condition could also become the patient with this latter type of condition. Thus, it appears that a patent ductus could only be detrimental from a hemodynamic aspect.

SUMMARY AND CONCLUSIONS

A study was made of total anomalous pulmonary venous connection associated with total anomalous pulmonary venous drainage, based on the reported records in 176 cases proved at necropsy or operation, or both. To this total were added 12 new cases. This series included cases both with and without associated cardiac defects.

This type of anomalous connection is more common in males. The anatomic pattern of anomalous venous connection is usually by way of a single anatomic location in the systemic venous system, more commonly by a single trunk, but sometimes by several pulmonary veins. Reports of 15 cases representing exceptions to this pattern were found; in these cases, the pulmonary venous return was by way of multiple locations in the venous system.

Data were analyzed in a selected group of 81 cases in which there was no major associated cardiac malformation, and in which the age of the patient, the site of anomalous connection, and the type of interatrial communication were known.

In general, death occurred in infancy or childhood, although exceptions were noted. The presence of short anomalous routes and large interatrial communications predisposed to longer survival times than did long routes and narrow interatrial communications.

The varying duration and intensity of cyanosis in patients with this anomaly, and even the complete absence of cyanosis, are emphasized because of the difficulty such variability may cause in differential diagnosis.

The clinical features of the anomaly have been presented, and the two main clinical patterns associated with the anomaly have been discussed.

ADDENDUM

Following completion of this report, our attention was called to the report of a case in which all the pulmonary veins from both lungs drained into the superior vena cava.[120]

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Annotations

Magnesium and the Cardiovascular System

Interest in the role of magnesium in the cardiovascular system was first stimulated by the work of Kruse and associates,[1] Sjollema,[2] and Greenberg and Tufts,[3] who demonstrated the occurrence of cardiac necrosis, fibrosis and calcification, vascular dilatation and nephrocalcinosis in the weanling rat fed a magnesium-deficient diet. Subsequently, similar lesions were produced by a magnesium-deficient diet in a variety of experimental animals.

Recent experimental studies in animals have been centered about the interrelationships between atherosclerosis, magnesium, and thyroxine. Vitale and his group[4-6] have shown that feeding atherogenic diets to weanling rats caused deposition of lipid in aorta and heart valves. Large amounts of dietary magnesium reduced this vascular sudanophilia, even though the levels of serum cholesterol rose. Administration of thyroxine to rats on an atherogenic diet decreased the levels of serum cholesterol, abolished the nephrocalcinosis, and reduced the intimal sudanophilia, even though the levels of serum magnesium remained low. Furthermore, these investigators found that adding atherogenic agents (cholesterol and cholic acid) to a diet containing 24 mg. per cent magnesium (enough for the normal requirement) produced typical symptoms and findings of magnesium deficiency. All symptoms and lesions were prevented by markedly raising the level of the dietary magnesium. Both in the rat with a low level of serum magnesium following use of an atherogenic diet, and after the feeding of thyroxine a decreased efficiency of oxidative phosphorylation of heart muscle mitochondria occurred. It has been established for several years that all ATP-catalyzed reactions have an absolute requirement for magnesium.[7] Furthermore, this group[8] has shown that an atherogenic diet given to weanling rats, with 20 per cent alcohol as the drinking fluid, produced higher levels of serum cholesterol and more deposits of lipid than when water was used. High levels of dietary magnesium lowered the amount of lipid deposited. Alcohol increased the requirement for magnesium in the basic diet, as did the addition of atherogenic agents.

A profound influence of the intake of protein on the requirement for magnesium has also been demonstrated in the rat,[9] because protein-depleted rats on a magnesium-deficient diet gained two times as much when the diet contained 7 per cent protein, as when the diet contained 14 per cent protein, in contrast to these diets with an adequate level of magnesium.

Studies with isotopic magnesium (Mg^{28}) in dogs has shown that the concentration of Mg^{28} was higher in the tissue of the heart than in any other tissue, and that this was not related to blood flow or muscle contraction.[10]

Cardiac necrosis has been produced in rats by the use of NaH_2PO_4 plus a steroid (Me-Cl-Col-AC), with marked decrease in the level of cardiac magnesium, and increase in the level of sodium and calcium.[11] It was thought that the cardiac lesions were due to low levels of cardiac magnesium. Myocardial infarct-like lesions and atherosclerosis were produced by other workers[12] through the use of substances of high-molecular weight. The lesions were prevented by the use of magnesium salts.

The work on magnesium in animals cannot, to date, be transferred directly to man. As for magnesium studies in man, it has been shown that, with aging, there is an increase in the content of calcium and magnesium in the human aorta.[13] A recent study showed higher than normal levels

of serum magnesium and lower levels of cholesterol in the Bantu, as compared to the European. A possible inverse relationship between the level of serum magnesium and the level of serum cholesterol was suggested, because the Bantu has very little coronary artery disease.[14]

The relationship of magnesium to clinical hypertension has been studied in a few patients with uncomplicated hypertension. The levels of serum magnesium were significantly lower, and the levels of serum sodium were higher, than in controls.[15] It was thought that this might represent increased adrenal cortical activity similar to that seen in primary aldosteronism, in which hypomagnesemia may occur. A magnesium-deficient diet in man has led to a transient loss of potassium, and retention of sodium and chloride.[16]

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Diagnostic Carbon Dioxide: Its Use in Review

It has been recognized for at least 40 years that injections of air or oxygen into the body can be of appreciable diagnostic or therapeutic value. Especially important examples of this are the diagnosis of adrenal tumors by perirenal or presacral injection of gas, intrauterine insufflation for diagnostic and therapeutic purposes, and the induction of pneumoperitoneum and pneumothorax. Progress along these lines has been seriously impeded by the occurrence from time to time of fatal, or nearly fatal, accidents due to the inadvertent entrance of gas into the circulatory sys-

tem. The value of injections of carbon dioxide as a safe substitute for air or oxygen has been recognized for many years (Rubin, Carelli, Cahill, Moore, Braselton). Its safety is dependent on its high degree of solubility in plasma (approximately twenty times that of air or oxygen), but its rapid absorption and dissipation have negated its use when long persistence of gas in any area is desired (e.g., pneumothorax). The safety of carbon dioxide was demonstrated in 1947, by Durant, Long and Oppenheimer, by means of large intravenous injections of this gas into dogs. Since then, further experiments in animals and injections into human beings have shown that pure carbon dioxide is safe whether injected into systemic veins or into the left ventricle or systemic arteries. As a result, at Temple University and in some other institutions, carbon dioxide has been substituted for air or oxygen for presacral injections, and it has been found to be just as satisfactory and completely safe. To my knowledge, there have been no fatalities reported from such use of carbon dioxide.

Aortic and pulmonary valves, atrioventricular rings, mitral and tricuspid valves, and even atrial septal defects, artificially created in dogs, have been viewed with remarkable clarity, depending upon the location of injection. At no time has any significant physiologic or chemical alteration been noted in the animals. Little or no work has been done in human beings in order to evaluate the role that carbon dioxide might play in the detection or demonstration of acquired or congenital intracardiac defects.

The major use in human beings, in addition to presacral injections, has proved to be in the study of pericardial disease, namely, pericardial effusions and pericardial constriction. The technique is simple and safe and may be done with a minimum of x-ray exposure. Thus, multiple studies may be done with safety. It may also be performed where the more expensive and complex angiocardiographic equipment is not available. Fifty to 100 cubic centimeters of *pure* carbon dioxide is injected into a large vein in the left arm, with the patient in the left lateral decubitus position. An ordinary posteroanterior film with a horizontal beam is taken immediately following injection, and is repeated as soon as the cassette can be changed. In the majority of instances a thin right atrial wall measuring 2 mm. or less is visible between the gas bubble in the right atrium and pulmonary parenchyma. In the presence of pericardial effusion this right heart border is thickened. Pericardial constriction or fibrosis is demonstrated by a straight margin or actual concavity of this region. The gas bubble in the right heart disappears rapidly through solution in pulmonary blood and excretion by expiration.

The total diagnostic value of carbon dioxide has yet to be explored. The implications are protean. But at least the veil has been removed from another "Dare Not" of the past.

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Ventricular Filling by Diastolic Suction

The return of systemic venous blood to the right atrium is usually considered to be effected by the vis a tergo produced by capillary pressure, aided by the aspiratory action of inspiration,[1] the contraction of skeletal muscles, and the increased capacity of the atrium produced by move-

ment of the atrioventricular valve toward the cardiac apex during ventricular systole. Left atrial filling is presumably due to pulmonary capillary pressure and apical movement of the mitral valve during ventricular systole. The forces responsible for ventricular diastolic filling are usually considered to be those of the vis a tergo of atrial pressure, augmented to a variable degree by atrial systole. However, recent observations by Bloom[2] on the filling and emptying of the excised rat heart beating in liquid, in the absence of venous return, have rekindled interest in the possibility that diastolic filling of the ventricles may be aided to an appreciable degree by ventricular diastolic suction.

As pointed out in Brecher's excellent critical review of the subject,[3] observations similar to Bloom's were made as early as 1823. However, the problem was not studied extensively in this century until interest was awakened by Bloom's observations.[2] Bloom and Ferris[4] demonstrated that the excised rat heart beating in liquid developed a positive left ventricular systolic pressure and a negative left ventricular diastolic transmural pressure, and was capable of filling and emptying repeatedly in the absence of vis a tergo produced by hydrostatic pressure, venous return, or atrial systole. Bloom and Ferris[4] also demonstrated that occlusion of the major venous return to the right atrium, produced by obstructing superior and inferior venae cavae and coronary sinus of the intact dog, was associated with negative diastolic right ventricular pressure. These workers also showed that obstruction of major venous return to the dog's left ventricle, produced by pulmonary venous occlusion, was associated with negative left ventricular diastolic transmural pressure. Brecher and Kissen[5] showed that when the ventricles of the dog's heart were emptied of blood by manual compression, a negative intraventricular pressure was recorded at these minimal ventricular volumes. Intraventricular pressure rose when liquid was added to the ventricles in increments of 1 ml., atmospheric pressure being reached at a mean ventricular volume of 5.1 ml. in the right ventricle and 8.2 ml. in the left.

Fowler, Couves and Bewick[6] have shown that negative left ventricular diastolic pressures develop in dogs subjected to rapid bleeding. Fowler, Shabetai and Braunstein[7] have observed that negative right and left ventricular diastolic transmural pressures are developed during cardiac tamponade in dogs. Fowler, Bloom and Ferris[8] demonstrated that the degree of negative diastolic pressure developed in the isolated beating rat heart was related to the vigor of the preceding systole. In these situations, venous return to the heart is compromised, and abnormally low ventricular volumes may be expected to be responsible for the negative diastolic transmural pressure developed. Brecher[9] has shown that the left ventricle of the dog is capable of filling by suction sufficiently to produce an aortic pulse when normal mean aortic pressure is maintained by a pump.

Brecher and Kissen[5] pointed out that negative ventricular diastolic pressures have been recorded only at abnormally low ventricular diastolic volumes, and that these measurements constituted no proof that ventricular suction occurred at normal diastolic ventricular volumes existing in the intact circulation. Brecher[9] also indicated, however, that ventricular diastolic suction may exist when ventricular diastolic pressure is positive, if there is a positive atrial pressure and ample blood available for ventricular filling. Thus, failure to demonstrate negative ventricular diastolic pressures in the intact animal does not exclude the possibility that ventricular suction exists as a mechanism aiding ventricular filling. By means of cineangiocardiography,[10] observations on the rate of change of ventricular volume in early diastole have indicated that ventricular filling is as rapid or more rapid than is ventricular ejection. These observations have suggested that such rapid change in ventricular diastolic volume is not likely due to vis a tergo alone.

Studies made to date have shown that the ventricles are capable of filling by diastolic elastic recoil following systolic contraction in the absence of vis a tergo. The presence of a potential aspirating force in the form of negative diastolic pressure has been shown only at abnormally low ventricular volumes associated with almost complete obstruction of venous return, hemorrhagic shock, or cardiac tamponade. Although Brecher's observations[9] suggest that some degree of ventricular filling by suction may occur at more normal ventricular diastolic volumes, no information is yet available as to the quantitative importance of this mechanism in the normal circulation.

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Therapeutic Fibrinolysis

The fibrinolytic mechanism of the blood has been subjected to extensive investigation from a considerable number of aspects.[1] There is fairly general agreement[2-4] that the mechanism consists of the activation of the globulin plasminogen (profibrinolysin) to an active proteolytic enzyme, plasmin (fibrinolysin). Plasminogen may be activated by many agents: the naturally occurring plasma activator, tissue activators (kinases), urokinase, enzymes such as trypsin, activators of bacterial origin such as streptokinase and staphylokinase, and a number of organic solvents such as chloroform. Inhibitors acting on this system either at the stage of activation (antiplasminogens) or against plasmin (antiplasmins) have been described and may be either naturally occurring or synthetic.

The idea of using this mechanism to therapeutic advantage has been actively explored in recent years.[5] Local application of fibrinolytic substances has been extensively employed in the treatment of indolent sores and chronic suppurative lesions, and many authors have described their results.[6-8] The much more difficult but potentially rewarding development of methods of inducing fibrinolysis on a systemic basis for the treatment of thromboembolic disease is making encouraging progress. Many workers have shown the idea to be practicable in the experimental animal,[6,9,10] and a number of methods in the human subject are currently being studied.[4] On a theoretical basis, systemic fibrinolysis could be achieved by the injection of agents causing an increase in plasma activator, by injecting plasminogen activators directly, by using plasmin itself, or by using other proteolytic enzymes, e.g., trypsin. The control of the level of the normal plasma activator by pharmacologic methods is as yet scarcely practicable, although the use of purified lipopolysaccharides of bacterial origin is being explored.[11] These substances are active pyrogens as well, but it seems that the pyrogenic action can be inhibited by antipyretics, without loss of the stimulus to fibrinolysis.

The use of plasminogen activators has much to commend it on theoretical grounds, since there is good evidence[4] that actual clot dissolution occurs as a result of the adsorption of activator on the fibrin in the interstices of the clot and the activation of the plasminogen of the clot in situ. Thrombolysis is influenced more by the surrounding concentration of activator than by that of plasmin. The activator used therapeutically so far has usually been purified streptokinase, and a number of workers have described their results with this technique.[12,13] Urokinase, the activator found in urine, should, for a number of reasons, be superior to streptokinase, but a sufficient amount of this substance in pure form is not yet available to permit clinical studies.

The intravenous injection of human plasmin has been employed.[14,15] As mentioned above, however, hyperplasminemia does not necessarily achieve thrombolysis, and it may well be that the effects of injected plasmin are due more to the action of the activator substance (usually streptokinase) used in making the plasmin and still present in the preparation.

The use of proteolytic enzymes other than plasmin, such as trypsin, has been largely given up,[4] mainly because it appears likely that effective thrombolytic action could only be attained in vivo at the risk of catastrophic general proteolytic effects.

At the present time, the most promising approach would seem to lie in the use of activator substances or of agents which increase the level of the physiologic plasma activator. Although this work is still fraught with many difficulties, the benefits of a method of effective thrombolysis are obvious and ensure that progress in this field will be watched with great interest.

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Gas Chromatography and Lipid Metabolism

It is now established that the nature of dietary fat exerts an important influence on the levels of serum cholesterol. Diets rich in unsaturated fatty acids are known to be associated with low levels of cholesterol, and diets rich in saturated fatty acids with high levels of cholesterol, although the mechanism is not yet understood. The study of this mechanism and other studies involving knowledge of the metabolic behavior of individual fatty acids have been handicapped in the past by the inadequacy of the analytical tools available. With the advent of gas chromatography, however, resolution and sensitivity of a new order of magnitude in the microanalysis of fatty acids is achievable, and many new studies have become possible.

As in the other chromatographic procedures, analysis by gas chromatography is based on repeated partition of the components of a mixture between a moving phase and a stationary phase. In this case, the moving phase is an inert gas, such as helium, nitrogen, or argon, and it is therefore required that it be possible to volatilize the substances to be analyzed. The stationary phase is a thermostable liquid with low vapor pressure selected for its affinity for these substances.

The usual column used in gas chromatography is a ¼-inch diameter glass or metal tube,

from 4 to 12 feet long, packed with an inert supporting material of high surface area on which the liquid phase is coated. Inert carrier gas is forced through this column at a nominal rate of 100 c.c. per minute.

When a mixture of long chain fatty acids, in the form of their methyl esters, is put on a column operated at 200° C., the various esters, which all have appreciable vapor pressure at this temperature, are carried through the column at different relative rates. The time taken by an individual ester to emerge from the end of the column depends on the column and the conditions under which it is operated. If these conditions are held constant, the time is characteristic of the ester and can be used to identify it. Although this time is generally related to the length of the chain and boiling point of the ester, separation of chemically different esters which differ only slightly in boiling point and molecular weight can be accomplished through proper choice of liquid phase. Polar liquid phases such as the polyester resins, for example, because of their selective affinity for unsaturated fatty acid esters, cause these esters to be retained on the column longer than saturated esters of the same chain length, despite the fact that the saturated esters have higher boiling points. Wide separation of physiologically interesting esters of the same chain length, such as stearic, oleic, linoleic, and linolenic acid esters, based on degree of unsaturation, is thus made possible.

Although the resolution obtained through the use of these "packed" columns is sufficient for many studies, considerable improvement in resolution has been obtained recently through the use of capillary columns, hundred-foot lengths of tubing with an internal diameter of 0.25 mm., the walls of which are coated with liquid phase. The small volume and small amount of liquid phase used in these columns, however, set an upper limit in the microgram range on the size of the sample that can be analyzed. Since the resolving power of both packed and capillary columns generally increases with the decrease in the size of the sample, their successful use has been facilitated or even made possible by the development of highly sensitive devices for the detection of the vapors.

Several of these devices are based on the sensitivity of the electrical properties of gases to small concentrations of impurities in the gas. Measurement of the electrical conductivity of burning hydrogen, argon in the presence of ionizing radiation, helium and argon under bombardment by thermal electrons at reduced pressures, and the properties of electrical discharges excited by the application of direct-current and radiofrequency fields have all been successfully used in the design of different high-sensitivity detectors.

The sensitivity of these detectors has made possible complete analysis of extremely small quantities of mixtures of fatty acid esters. While maximizing the resolving power of the columns, this high sensitivity also had the effect of making feasible many studies previously not possible because of the limited availability of fatty acids from biologic specimens. Concentrations of as little as one molecule of ester in hundreds of millions of molecules of carrier gas can be accurately detected and quantitated. It is now possible to do a complete analysis of fatty acids on as little as 1 microgram of material in which individual components of as little as 0.01 microgram can be quantitated precisely. To the biochemist and to the clinician interested in the study of lipid metabolism, this means, for example, that a complete analysis of the fatty acids in the individual lipid compartments or classes can be carried out on the usual venipuncture specimens of blood or in small biopsy specimens.

The combination of analysis by gas chromatography and the use of radioactive tracers promises to facilitate studies of the dynamics of the metabolism of fatty acids. There are methods now available for assaying the individual fatty acids for radioactivity as they leave the analytical column, at the same time that their amount is determined. Since it is possible to recover individual esters following analysis, gas chromatography can also be used micropreparatively to provide small quantities of purified carbon-14 labeled fatty acids.

Because many different classes of compounds are volatile or have volatile derivatives, the possible applications of analysis by gas chromatography are many. It has already proved valuable in biochemical and physiologic studies involving the identification and analysis of amines, alcohols, hydrocarbons, and short chain fatty acids, as well as in those concerned with the long chain fatty acids, on which much interest has been focused. More widespread application of the technique to analysis of the respiratory gases, anesthetic gases, and other physiologically significant volatile

compounds is predictable. Application of the method to the analysis of steroids and other compounds of higher molecular weight is presently being explored.

The technique of gas chromatography as applied to the analysis of fatty acids has now been sufficiently developed to permit its establishment and use at many centers at which research on lipids is being carried out. Studies have begun to appear that include data showing the exact composition of dietary fats used in metabolic studies and the exact fatty acid composition of the various classes of serum and tissue lipids. We can expect studies of the dynamics of the metabolism of individual fatty acids in phospholipids, triglycerides, and cholesterol esters, augmenting and supplemented by data obtained through the use of radioactive tracers. Predictably, the over-all impact upon research on lipid metabolism and the relationship of lipid metabolism to atherosclerosis will be great.

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Vascular Balances

The observation was made several years ago that an acute increase in the volume of blood contained in one part of the body was generally accompanied by compensatory decreases in the volume contained in some other part of the body. This redistribution of the total blood volume is an obvious consequence of the very limited rate at which the *total* blood volume in the body can be expanded. In a circulatory system of rapidly variable capacity but with a relatively fixed blood content, some compensatory device of this sort is essential. This phenomenon was termed "hemometakinesia."[1] More detailed studies indicate that any chronic significant increase in blood volume in any part ultimately results in an increase in the total blood volume. Under certain conditions, defined by Sjostrand[2] and others, the total blood volume is slowly modified to take care of the increases, even though they are local.

Corresponding adjustments and balances of the *volume flow* through the various parts of the vascular bed have been taken for granted. Here the picture is not quite so clear-cut since there is a mechanism for the rapid modification of the total blood flow in the organism even under acute circumstances. That is, an increase in the blood flow through a certain area of the body is frequently accompanied by an increase in the cardiac output, so that no compensatory decrease in blood flow through parallel circuits need occur. However, under conditions of extreme increase in blood flow in particular tissues, the parallel circuits may show a diminished blood flow to conserve or minimize the modification of the cardiac output. This type of compensatory decrease in blood flow through one area in order to satisfy the demand in another area becomes apparent when the *total* arterial inflow is physiologically limited, or, especially, when some pathologic determinant imposes an absolute maximum value for total blood flow into an area. Recently,[3] we called attention to several clinical conditions in which this may occur. Such a redistribution or diversion of blood flow must always be considered in the treatment of local arterial insufficiencies, so that the clinical picture is not inadvertently worsened by shunting the blood flow from an already ischemic area by dilation elsewhere.

Diversion of blood flow may occur by either of two different mechanisms. In the simplest case an increase in flow through a dilated area increases the run-off from the arterial tree and diminishes the mean arterial pressure. If the parallel circuits leaving this same arterial pool show no corresponding dilation, the blood flow through them must decrease. This simple type of mechanical redistribution of blood flow is most frequently encountered in extremities in which the arterial inflow is embarrassed or absolutely limited by some obstruction of the arterial system. A more complex and probably more physiologic mechanism is that which involves an active compensatory vasoconstriction in certain beds simultaneous with a dilation in the bed under immediate study. Several reflexes of this kind have been described in the literature. For example, increases in blood flow through muscle or through the skin may be accompanied by decreases in renal blood flow. The underlying physiologic mechanism would probably involve something as follows: The increase in blood flow through the skin or muscle modifies the cardiovascular dynamics to trigger appropriate receptors, and these, in turn, set off compensatory vasoconstrictor

as well as appropriate cardiac reflexes. Direct measurements have shown that exercise will not decrease renal blood flows measurably until the demands of the exercising muscle are quite high[4] and exceed reasonable adjustment of the cardiac output. It is also possible that the increase in blood flow through one area might be compensated by a smaller but generalized vasoconstriction throughout the body. This sort of physiologic reflex compensation for locally increased blood flow is likely, even though it has not been frequently demonstrated.

We should like to return, however, to the simple mechanical diversion which may have the most significant clinical implications. It is important to recognize that the factors governing blood flow through various tissues are not in all cases identical, that the responses of the several tissues may differ when challenged by a given drug, and that the responses of the blood vessels of even the same tissue may be modified by pathologic conditions. Thus, an attempt to increase blood flow in an ischemic limb may, in fact, increase the blood flow through only a part and, by simple mechanical diversion, actually cause a profound embarrassment of the circulation through the remainder of the tissues. Unfortunately, the vessels which cannot respond to a drug or procedure by vasodilation may be, in point of fact, in a tissue already suffering from ischemia, so that a "dilating" procedure could aggravate rather than improve the situation.

Much work is needed on the problem of the sensitivities and reactivities of blood vessels in specific tissues under normal and clinical conditions, in order to assess the implications of this type of diversion. Studies of this kind, of course, are currently in progress in many laboratories throughout the world; the findings will have to be correlated and their implications carefully read before a final analysis can be made.

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Shock Following Myocardial Infarction

The development of shock in acute myocardial infarction produces a hazardous condition with a high mortality rate. It appears that among the factors which affect the prognosis, the duration of shock prior to treatment is of great importance. If relief of hypotension is achieved promptly by the use of vasopressor substances, the prognosis appears to be more favorable. Thus, Miller and Moser[1] pointed out that only 3 out of 10 patients survived, in whom shock following myocardial infarction was known to have been present for over 4 hours, whereas 10 out of 17 patients treated survived when shock was present for less than 1 hour. In a series of 30 such patients treated with l-norepinephrine by Sampson and Zipser,[2] an immediate survival rate of 67 per cent was noted. In this group, the duration of shock before treatment averaged 1.8 hours in those who survived, and 4.0 hours in those who died. Griffith and his associates,[3] in treating shock due to recent myocardial infarction by vasopressor substances and other supplementary means, noted that 60 patients treated within 3 hours of the onset had a mortality rate of only 13 per cent. By contrast, 74 patients who were treated after the lapse of a 3-hour interval showed a mortality rate of 76 per cent.

The classic experiments of Wiggers[4] in animals indicate that profound myocardial damage and irreversible circulatory failure develop when hemorrhagic shock is prolonged for a considerable period of time. Corday and his co-workers[5] have also presented evidence revealing the profound effect of hypotension in reducing myocardial contractility and in decreasing collateral coronary flow. More recently, Savranoglu and associates[6] have pointed out that after a period of 60 minutes

in animals, sustained tissue anoxia appeared to produce irreversible damage. Moreover, Calvia and associates[7] have shown that the decreased availability of myocardial oxygen and the decrease in effective coronary flow which occurs with falling blood pressures are readily reversible with l-norepinephrine.

The clinical lesson to be learned from these studies in patients and from the laboratory seems clear. The development of shock in acute myocardial infarction produces an acute clinical experiment in which survival often is linked to a critical time factor. If effective mean aortic pressure is promptly restored toward normal, with an associated elevation in coronary flow and improvement in myocardial function and collateral flow, the patient may survive the episode. On the contrary, if the shock is unrecognized and treatment is delayed in these patients, irreversible changes may develop in the heart muscle, associated with a high mortality rate, and the frequent development of terminal myocardial failure.

The conclusion to be drawn from all of this is that the blood pressure and heart rate are two of the parameters which must be followed with the utmost care during the initial hours and days following the development of acute myocardial infarction. Constant observation of the patient for clinical signs of shock (such as sweating, pallor, weakness, etc.) is also highly important. The problem is further complicated by the fact that many such patients are treated in an oxygen tent and are kept quiet by sedation and analgesics. Under such circumstances, there is often a tendency to avoid disturbing them to measure their blood pressure and heart rate. With the development of monitoring devices, it may well develop in the future that such patients will generally have their blood pressure and pulse recorded automatically, so that warning signals may be flashed if hypotension and/or arrhythmias develop. Such an approach may lead to a further reduction in the mortality rate of patients suffering from acute myocardial infarction.

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Letter to the Editor

615 Eleventh Street North
St. Petersburg 5, Fla.
March 18, 1960

To the Editor:

I cannot allow Dr. Don Fisher's letter in the March, 1960, issue to pass without comment. It was my privilege, affectionately recalled as with Dr. Whittlesey, to have had Dr. Horace Korns for a teacher. His method of separating left ventricular hypertrophy from pericardial effusion was based upon the flare of the costal margins. He credited Hoover with demonstration of this phenomenon, and in his hands it was a convincing maneuver. But this is not the question.

The question is how the young man finds it possible to go beyond demonstration of what he conceives to be an error in the past, by reflecting on the individuals who made those contributions. It is one of the tragedies of American medical education today that we have so few teachers of the caliber of Horace Korns. That he was such a teacher is evidenced by Dr. Whittlesey's letter, and you may be sure that there would be hundreds of others who would agree that he was worthy of our emulation. It could be that the technique is difficult to learn, much more difficult than asking for a chest film. It is nonetheless worth while and will return dividends to those who understand and apply the valid mechanisms which underlie its practical usefulness.

Robert Johnson Needles, M.D.

Announcements

THE FIRST INTERNATIONAL SYMPOSIUM OF CYBERNETIC MEDICINE, organized by the International Society of Cybernetic Medicine, will be held in Naples, Italy, Oct. 2-4, 1960, under the presidency of Prof. Aldo Masturzo, of Naples University.

The general theme of the Symposium will be: "The Introduction of Cybernetic Methods in Modern Medicine."

For further information, write to Prof. Renato Vinciguerra, Secretary, S.I.M.C., Via Roma 348, Naples, Italy.

THE SIXTH INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, organized by the International Society of Internal Medicine (President, Sir Russell Brain, F.A.C.P. Hon., London), will be held in Basle, Switzerland, Aug. 24-27, 1960. President of the Congress is Prof. Dr. A. Gigon, Basle.

The principal subjects of the Congress will be "Pathogenesis and Therapy in Edema" and "Enzyme Regulations in the Clinic." Panels will discuss: Interstitial Nephritis; Nephrosis; Diuretics; Diagnostic Value of Enzymes; Therapeutic Indications of Enzymes; Serology in Rheumatic Diseases; Instruction in Internal Medicine. There will also be lectures on subjects of the lecturers' own choice. Seventy leading internists from all over the world will take part in the main scientific program by reading their papers or joining in the panel discussions. The official languages of the Congress will be German, French, and English, and there will be simultaneous translation of the principal lectures.

Program and registration forms for the Congress may be obtained from Prof. Dr. H. Ludwig, Secretary, Sixth International Congress of Internal Medicine, Steinentorstrasse 13, Basle 10, Switzerland.

THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY will offer the third biannual course on "Modern Research Methods in Biology and Medicine," from July 5 to 15, 1960. This is an opportunity for intensified study of important recent advances in electronics and other fields of instrumentation and their application to the fields of medicine and biology.

The Special Summer program will be of particular interest to medical research workers and biologists as well as to research administrators. The material in this course will be presented in the form of "Instrumentation Elements." This method of teaching offers considerable advantages over older methods. Knowledge of higher mathematics is not a prerequisite for the course.

Instrumentation has led to revolutionary developments in many of the physical sciences; it will be of similar importance in the life sciences, leading to new research methods and diagnostic procedures.

The 1960 program will be under the direction of Dr. Kurt S. Lion, Associate Professor of Applied Biophysics. Lectures will also be given by specialists from Massachusetts Institute of Technology and other universities.

All facilities at M.I.T. will be open to the members of this course, and housing will be available in the Institute's dormitories.

Application forms and full information may be obtained from Dr. James M. Austin, Director of the Summer Session, Room 7-103, Massachusetts Institute of Technology, Cambridge 39, Mass.

AN INTERNATIONAL SYMPOSIUM, entitled "The Etiology of Myocardial Infarction," will be held at the Henry Ford Hospital on Nov. 16-18, 1961. Those interested may write to Thomas N. James, M.D., Henry Ford Hospital, Detroit 2, Mich.

AMERICAN
HEART
JOURNAL

An international publication for the study of the circulation

GEORGE E. BURCH, M.D., Editor

Assistant Editors: WILLIAM D. LOVE, M.D.
PAUL B. REASER, M.D.
JOHN H. PHILLIPS, M.D.

1430 Tulane Avenue, New Orleans 12, Louisiana

Published by The C. V. Mosby Company,
3207 Washington Boulevard, St. Louis 3, Mo.

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VOLUME 59

JANUARY-JUNE, 1960

VOLUME 59
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Printed in the
United States of America

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Vol. 59, No. 6, June, 1960. American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis 3, Mo. Second class postage paid at St. Louis, Mo., and at additional offices. Subscription rates: United States and Its Possessions $13.00, Students $6.50; Canada, Latin-America, and Spain $13.50; Students $7.00; Other Countries $14.50, Students $8.00 Single copies, $2.00 postpaid. Printed in the U. S. A. Copyright © 1960 by The C. V. Mosby Company.

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1430 Tulane Avenue, New Orleans 12, Louisiana

Published by The C. V. Mosby Company,
3207 Washington Boulevard, St. Louis 3, Mo.

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Publication Order.—This Journal is published monthly. The monthly issues form two semiannual volumes; the volume index is in the last issue of the volume—in the June and December issues.

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safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2,* the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

'Clarin', which is heparin in the form of a *sublingual tablet,* has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

References: **1.** Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. **2.** Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. *7*:225 (Apr.) 1959. **3.** Stutman, L. J., and George, M.: Clin. Res. *7*:225 (Apr.) 1959. **4.** Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. **5.** Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. **6.** Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. **7.** Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. **8.** Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

Clarin*

(sublingual heparin potassium, Leeming)

Fig. 1

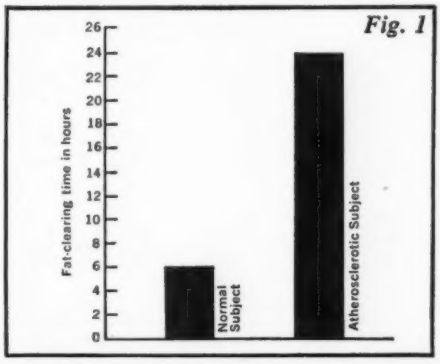


Fig. 2

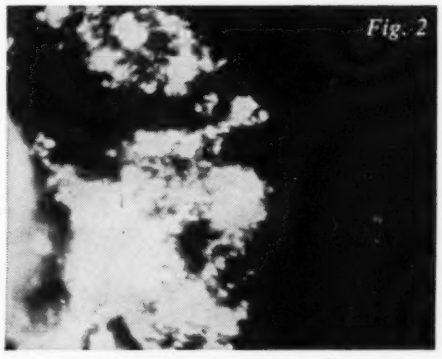
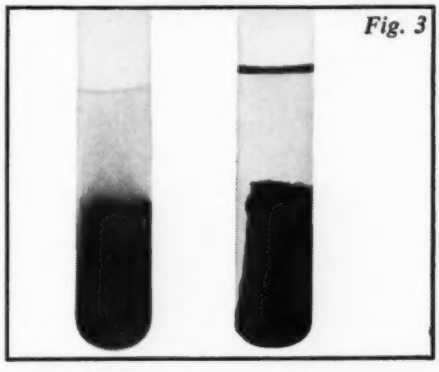


Fig. 3



Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: 'Clarin' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc.
New York 17, N. Y.

90% of anxious, agitated and apathetic office patients calmed without drowsiness and with normal drive restored...

on one or two 0.25 mg. tablets b.i.d.:

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■ PERMITIL is virtually free from side effects at recommended dosage levels.

■ Patients become calm without being drowsy and normal drive is restored.

■ Onset of action is rapid; effect is prolonged. ■ PERMITIL does not potentiate barbiturates or non-barbiturate sedatives and can be used with impunity with such agents.

How to Prescribe PERMITIL: The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day (taken morning and afternoon). Increase to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms which are uncontrolled at lower dosage. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. Complete information concerning the use of PERMITIL is available on request.

Supplied: Tablets, 0.25 mg., bottles of 50 and 500.

*Recent compilation of case reports received by the Medical Department, White Laboratories, Inc.

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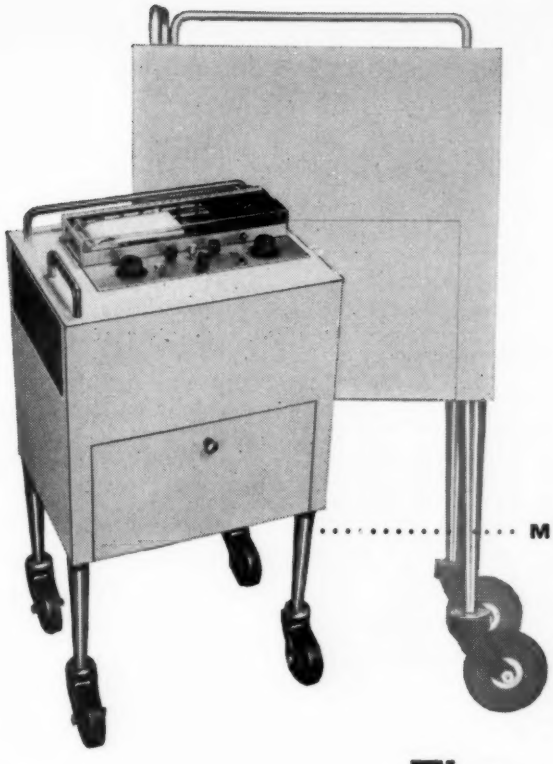

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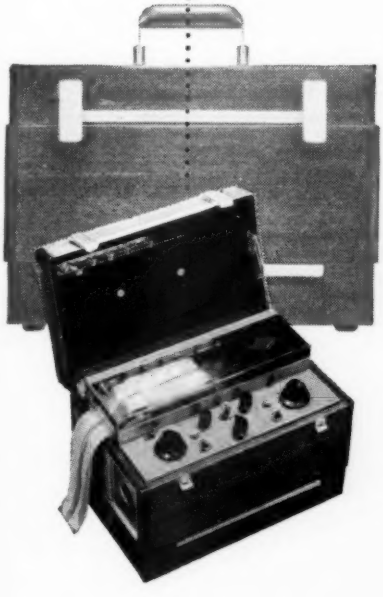

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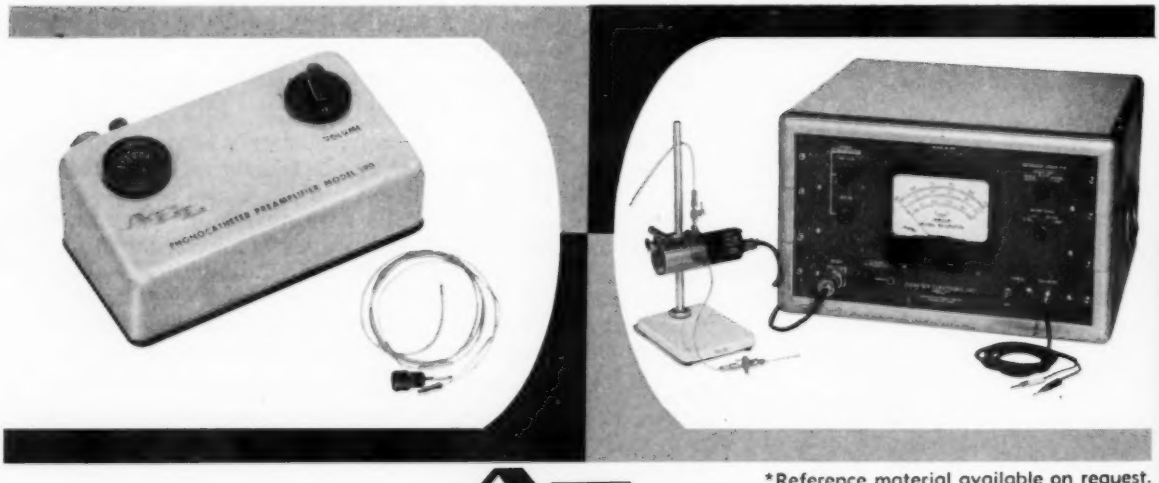

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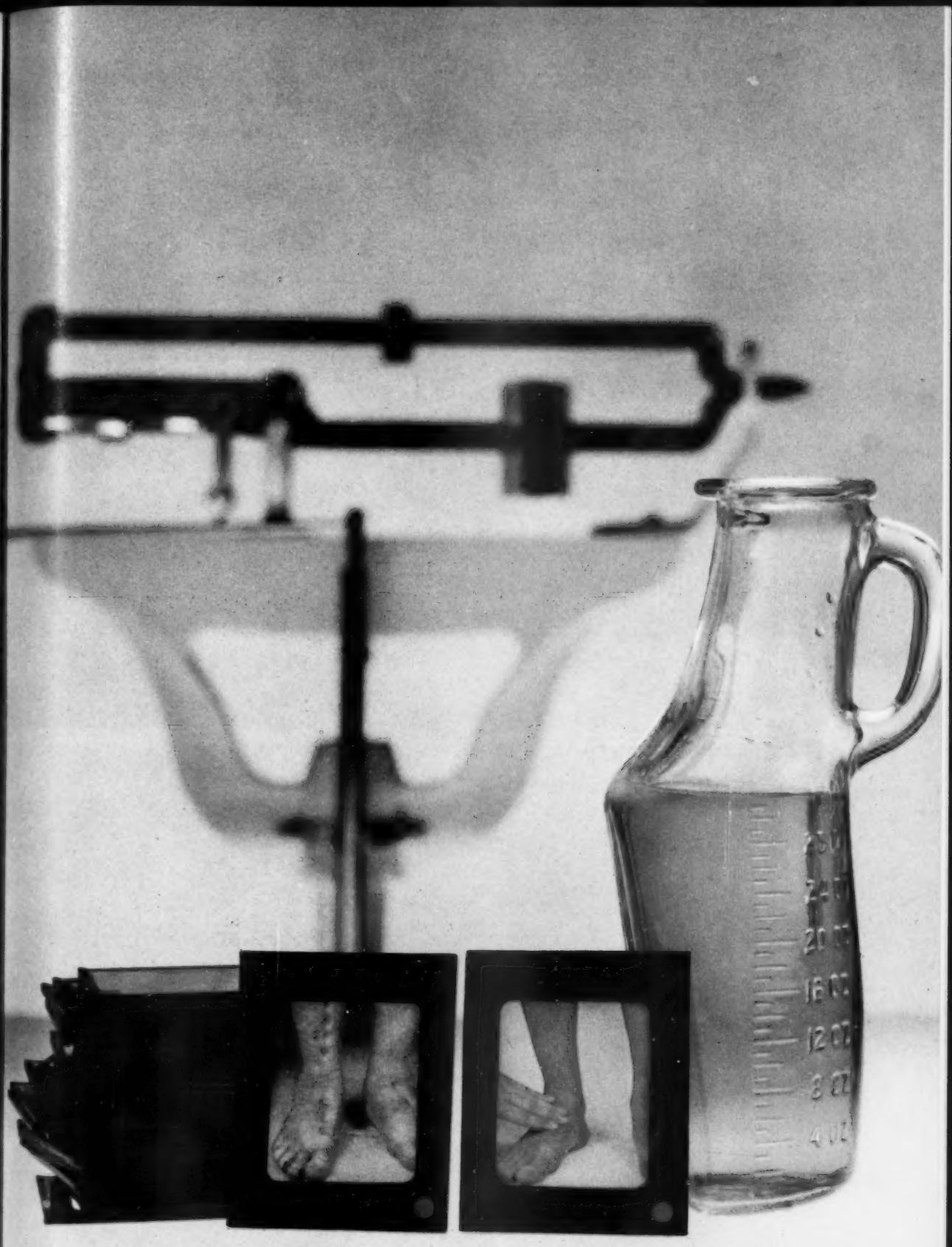

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*Brest, A. N., and Likoff, W.: Am. J. Cardiol. *3*:144 (Feb.) 1959.

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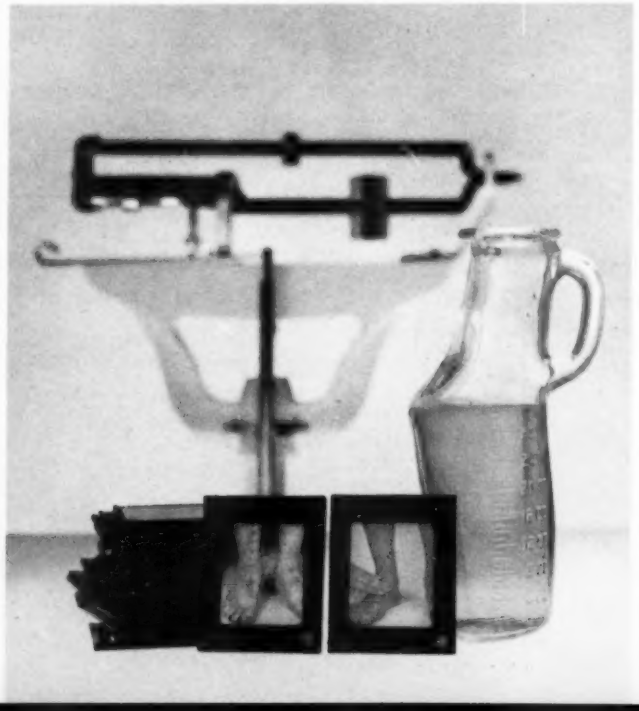
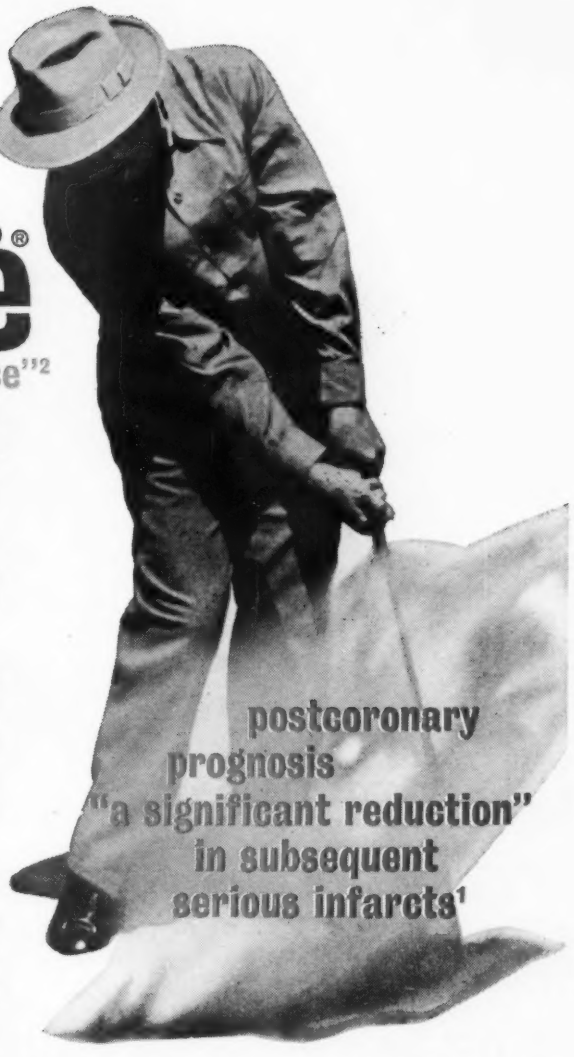


Danilone (Phenindione, Schieffelin) ®

"the anticoagulant drug of choice"[2]



When DANILONE was administered to 33 postmyocardial infarct patients, only two thromboembolic episodes occurred in two patients in 565 patient-months. Five such episodes in 50 patient-months occurred in four patients who had stopped taking anticoagulants.[3]

"twice as fast in reaching therapeutic levels"[4] In 117 patients, the average time DANILONE required to attain therapeutic levels was less than 36 hours.[4] With bishydroxycoumarin, two to four days are required for equal effect.[5]

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"a reputation for safety"[7] DANILONE, unlike the coumarin derivatives, has a short recovery period and no cumulative action.[5,8,9] As a result, DANILONE "... can be administered with reasonable safety in the presence of many conditions which would contraindicate the use of Dicoumarol."[6]

"a lack of toxic reactions"[3] Because of its extremely low incidence of toxicity,[2,4,9] and "... the apparent safety factor of a wide spread between therapeutic and toxic dose, it is felt that phenyldanedione [phenindione] is the anticoagulant drug of choice."[2]

"inexpensive"[5] DANILONE is the least expensive anticoagulant available today. Maintenance cost is as little as three cents a day. In addition, its stability of effect permits fewer prothrombin-time tests,[9] saving the patient additional costs.

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References: 1. Pickering, G., et al.: Brit. M. J. 1:803 (Mar. 28) 1959. 2. McCabe, E. S., and Fittipoldi, J., Jr.: Am. Pract. & Digest Treat. 4:765, 1953. 3. Drinan, F. W., et al.: Am. Heart J. 53:284, 1957. 4. Harper, B. F., and Johnson, R.: J.M.A. Georgia 45:149, 1956. 5. Wood, J. E.; Beckwith, J. R., and Camp, J. L., III: J.A.M.A. 159:635 (Oct. 15) 1955. 6. Sise, H. S.; Maloney, W. C., and Guttas, C. G.: Am. Heart J. 53:132, 1957. 7. Newcomb, T. F.: New England J. Med. 260:545 (Mar. 12) 1959. 8. O'Connor, W. R.; Thompson, C. E., and Baker, L. A.: Quart. Bull. Northwestern Univ. M. School 26:193 (Fall) 1952. 9. Toohey, M.: Brit. M. J. 1:650 (Mar. 21) 1953.

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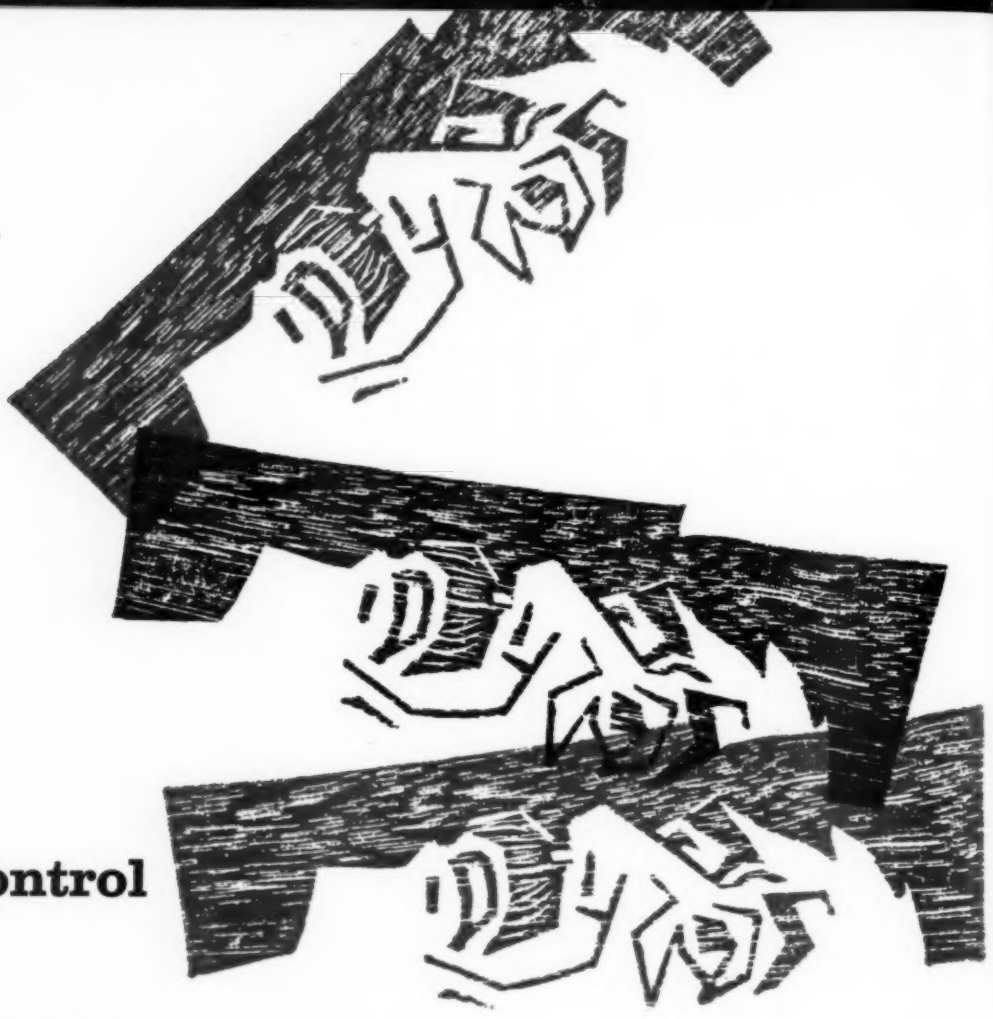

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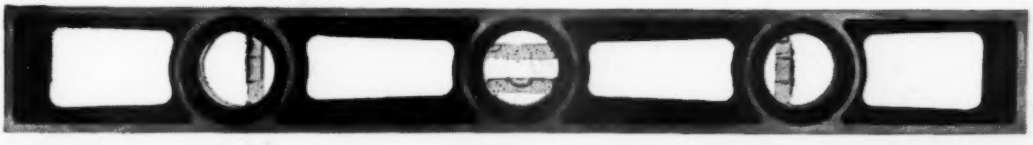

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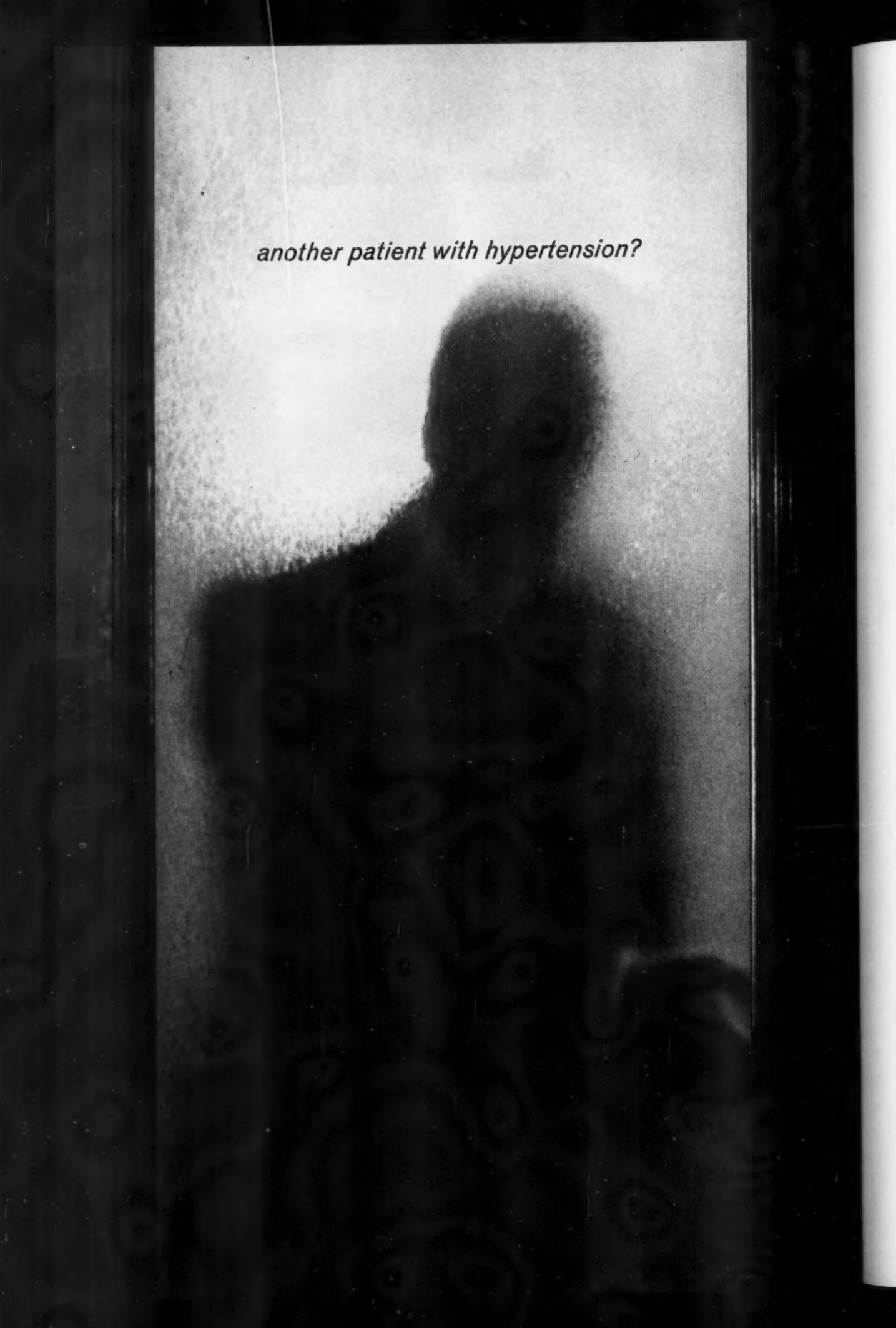
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(In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

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25 mg. HydroDIURIL, 0.125 mg. reserpine. One tablet one to four times a day.

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If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

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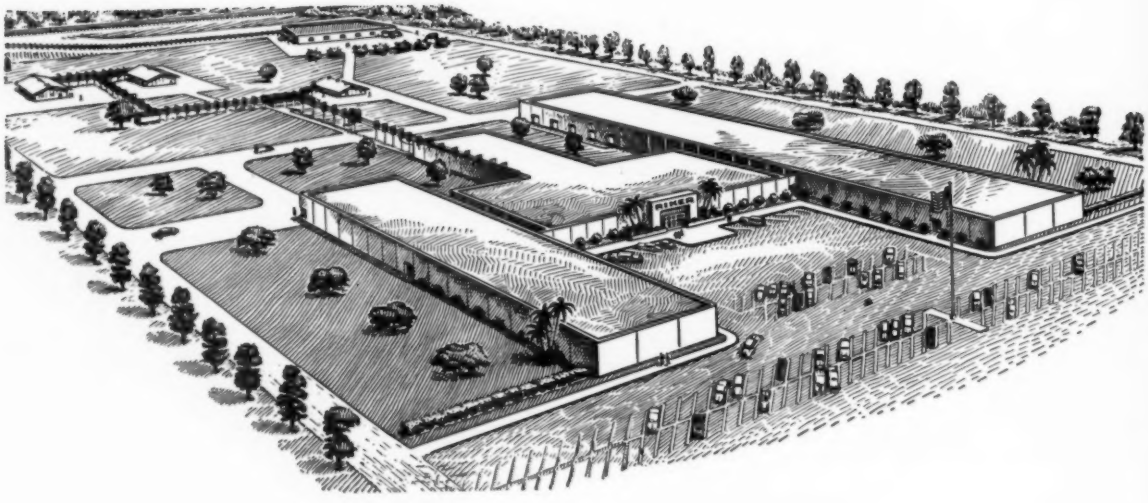

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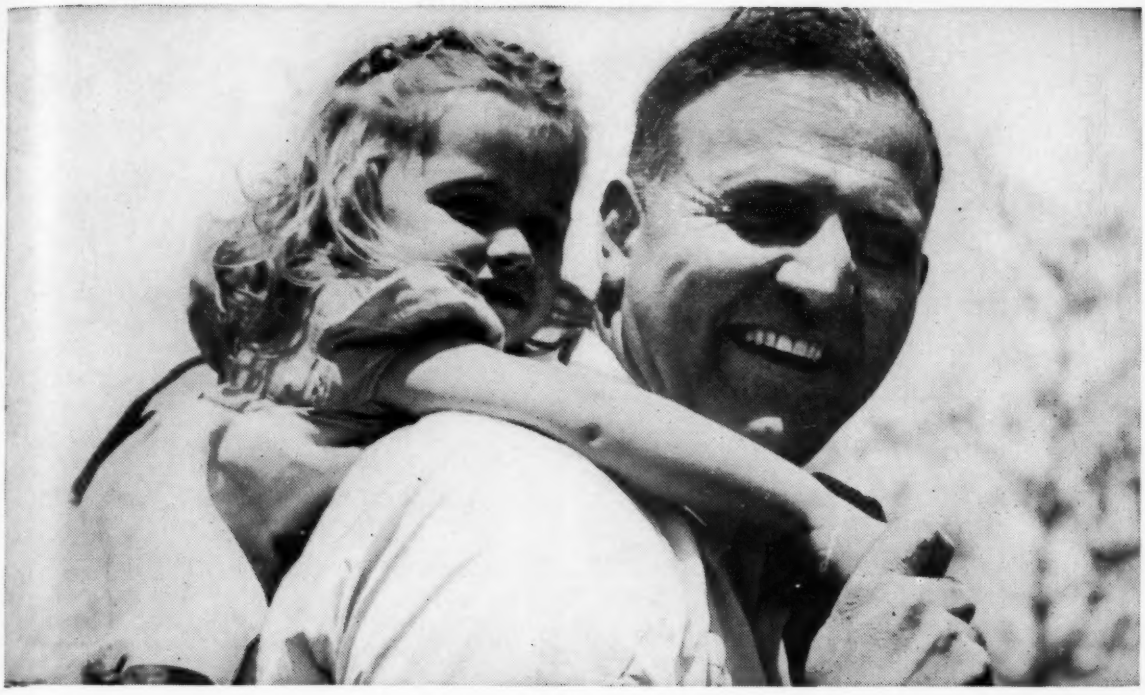

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prolonged, sustained-action of vasodilating pentaerythritol tetranitrate (PETN) 30 mg., and sedative secobarbituric acid 50 mg.

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2. Kupersmith, I. H.: International Record of Medicine, Vol. 171 No. 10 (Oct.) 1958.
3. Berry, J. W., and Roach, T. C.: Circulation, Vol. 17, No. 6 (June) 1958.

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CLINICAL OPINION

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CLINICAL OPINION

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CLINICAL OPINION

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Erythrol Tetranitrate Sublingual Tablets

NEW

5 mg., scored

15 mg., scored

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1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

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On bread, toast and crackers Emdee Margarine has the same taste as other fine spreads, and a firm, smooth texture. It brings back the familiar flavor to baked potatoes, vegetables and popcorn. It can be used for braising, baking, roasting and sautéing, and in white sauces and frostings. It has won praise from Home Economics experts, who found that Emdee Margarine is a high-quality shortening.

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REFERENCES: 1. Terman, L. A.: Dietary management of hypercholesterolemia, Geriatrics *14*:111 (Feb.) 1959. 2. Boyer, P. A.; Lowe, J. G.; Gardier, R. W., and Ralston, J. D.: Effect of a practical dietary regimen on serum cholesterol level, J.A.M.A. *170*:257 (May 16) 1959. 3. Vail, Gladys E.: Cooking with fats high in polyunsaturated fatty acids, J. Am. Dietet. A. *35*:119 (Feb.) 1959. 4. Jolliffe, N.; Rinzler, S. H., and Archer, M.: The Anti-Coronary Club; including a discussion of the effects of a prudent diet on the serum cholesterol level of middle-aged men, Am. J. Clin. Nutrition *7*:451 (July-Aug.) 1959.

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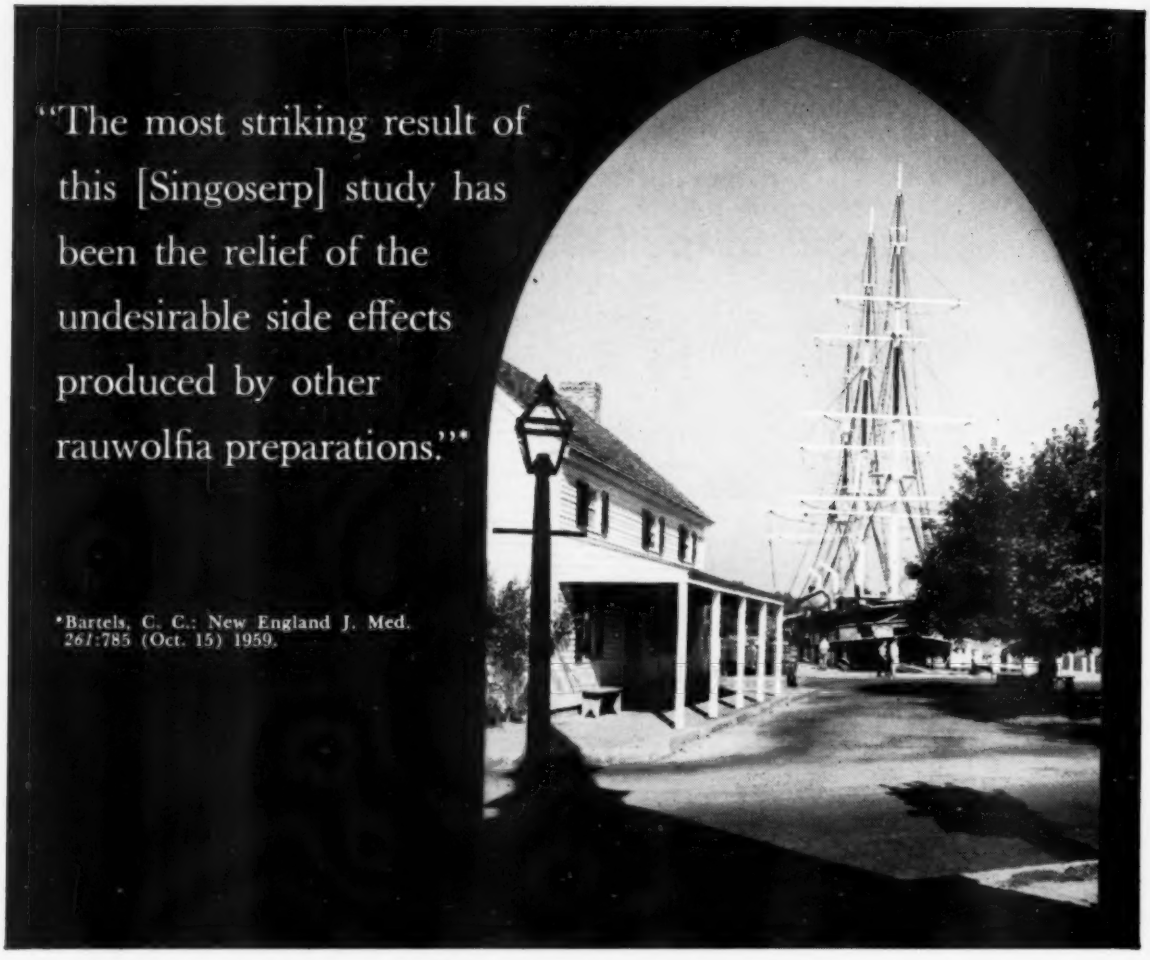
"The most striking result of this [Singoserp] study has been the relief of the undesirable side effects produced by other rauwolfia preparations."*
*Bartels, C. C.: New England J. Med. 261:785 (Oct. 15) 1959.

results you can confirm in your practice:

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Side Effects	Incidence with Prior Rauwolfia Agent	Incidence with Singoserp
Depression	11	1
Lethargy or fatigue	5	0
Nasal congestion	7	0
Gastrointestinal disturbances	2	2
Conjunctivitis	1	0

(Adapted from Bartels*)

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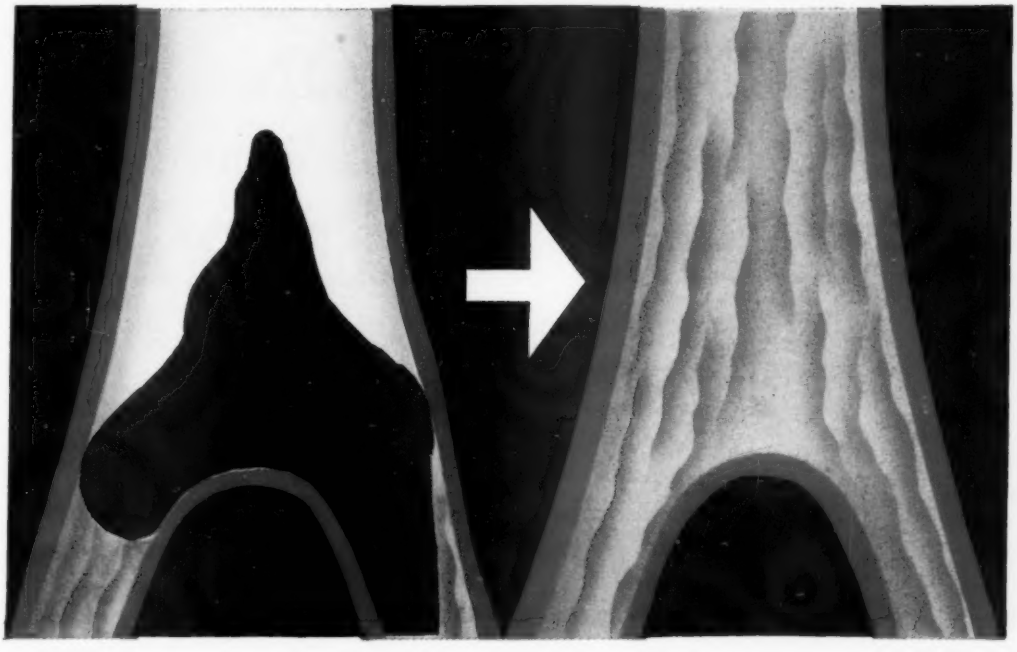

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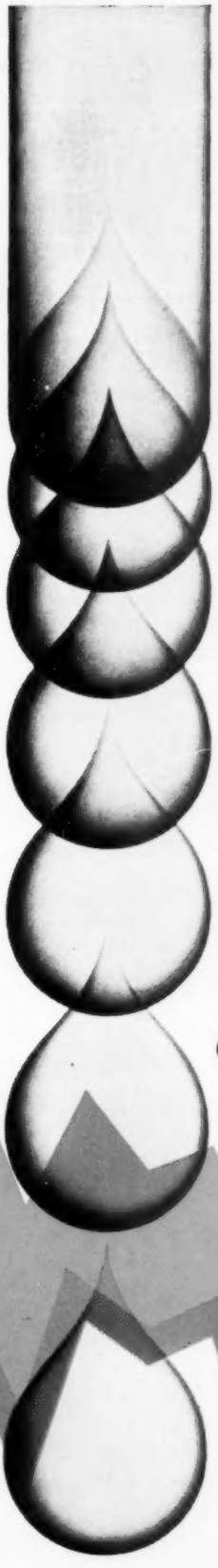

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lesser loss of potassium

A new antihypertensive-saluretic, Hygroton, now enables still more effective control of hypertension and edema.

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Because it is more prolonged in action than any other diuretic,[1] Hygroton affords a smoother, more evenly sustained response.

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Hygroton produces only minimal potassium loss . . . affords a better sodium-potassium ratio than other saluretics.[3]

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As a rule, with Hygroton, restriction of dietary salt is unnecessary.

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Sustained control without side reactions.

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Copious diuresis without electrolyte imbalance.

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References:
(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication.

Geigy, Ardsley, New York HY 234-60

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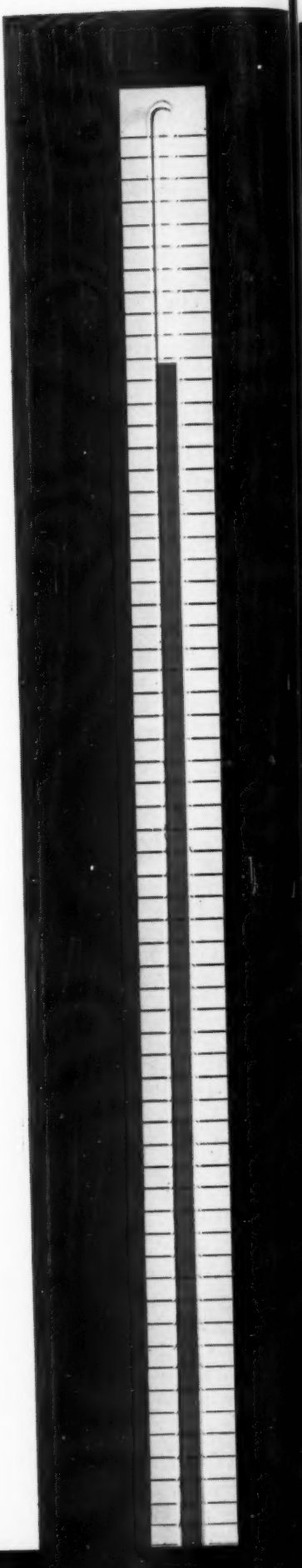

New Rautrax-N results in prompt lowering of blood pressure.[1] Rautrax-N, a new antihypertensive-diuretic preparation, provides improved therapeutic action[1] plus enhanced diuretic safety for all degrees of essential hypertension. A combination of Raudixin and Naturetin, Rautrax-N facilitates the management of hypertension when rauwolfia alone proves inadequate, or when prolonged treatment, with or without associated edema, is indicated.

Naturetin, the diuretic of choice, also possesses marked antihypertensive properties, thus complementing the known antihypertensive action of Raudixin. In this way a lower dose of each component in Rautrax-N controls hypertension effectively with few side effects and a greater margin of safety.[1-16]

Other advantages are a balanced electrolyte pattern[1-16] and the maintenance of a favorable urinary sodium-potassium excretion ratio.[2-16] Clinical studies[1-5] have shown that the diuretic component of Rautrax-N—Naturetin—has only a slight effect on serum potassium. The supplemental potassium chloride provides additional protection against potassium depletion that may occur during long term therapy.

Rautrax-N may be used independently or with other antihypertensive drugs, such as ganglionic blocking agents, veratrum or hydralazine, when needed for the occasionally difficult patient.

Supply: Rautrax-N—capsule-shaped tablets providing 50 mg. Raudixin (Squibb Rauwolfia Serpentina Whole Root) and 4 mg. Naturetin (Squibb Benzydroflumethiazide), with 400 mg. potassium chloride.

Dosage: For initial therapy, the suggested dosage is 1 to 4 Rautrax-N tablets daily after meals. If the higher amounts are needed, daily dosage should be divided into 2 doses given every 12 hours. However, dosage should be initiated at a low level, which may be increased after intervals of several days, if necessary, until the desired response is obtained. For maintenance therapy, 1 or 2 Rautrax-N tablets daily should prove adequate; however, daily maintenance dosage may range from 1-4 Rautrax-N tablets. Note: In hypertensive patients already on ganglionic blocking agents, veratrum or hydralazine, the addition of Rautrax-N will require an immediate dosage reduction of each of these agents by at least 50 per cent. The same dosage reduction applies when any of these agents is added to the Rautrax-N regimen. Literature available on request.

References: 1. Reports to the Squibb Institute, 1960. 2. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 3. Stenberg, E. S., Jr.; Benedetti, A., and Forsham, P. H.: Op. cit. 5:46 (Feb.) 1960. 4. Fuchs, M.; Moyer, J. H., and Newman, B. E.: Op. cit. 5:55 (Feb.) 1960. 5. Marriott, H. J. L., and Schamroth, L.: Op. cit. 5:14 (Feb.) 1960. 6. Ira, G. H., Jr.; Shaw, D. M., and Bogdonoff, M. D.: North Carolina M. J. 21:19 (Jan.) 1960. 7. Cohen, B. M.: M. Times, to be published. 8. Breneman, G. M. and Keyes, J. W.: Henry Ford Hosp. M. Bull. 7:281 (Dec.) 1959. 9. Forsham, P. H.: Squibb Clin. Res. Notes 2:5 (Dec.) 1959. 10. Larson, E.: Op. cit. 2:10 (Dec.) 1959. 11. Kirkendall, W. M.: Op. cit. 2:11 (Dec.) 1959. 12. Yu, P. N.: Op. cit. 2:12 (Dec.) 1959. 13. Weiss, S.; Weiss, J., and Weiss, B.: Op. cit. 2:13 (Dec.) 1959. 14. Moser, M.: Op. cit. 2:13 (Dec.) 1959. 15. Kahn, A., and Grenblatt, I. J.: Op. cit. 2:15 (Dec.) 1959. 16. Grollman, A.: Monographs on Therapy 5:1 (Feb.) 1960.

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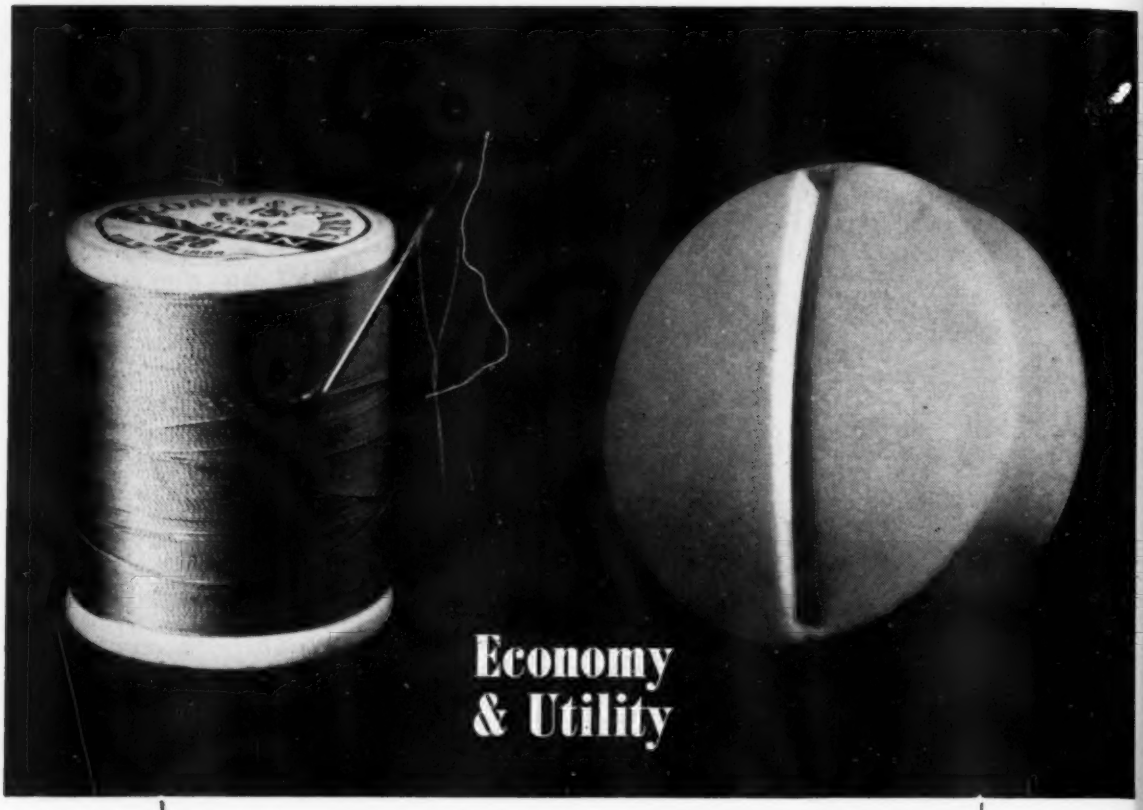

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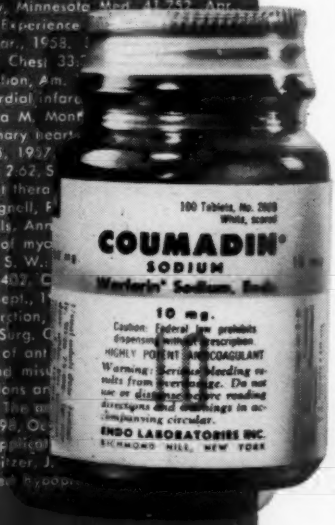

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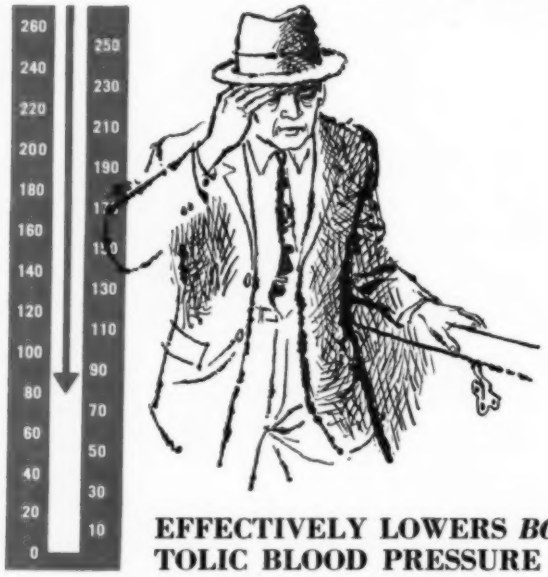

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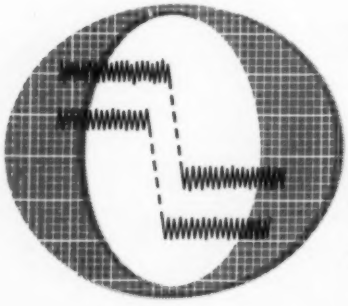

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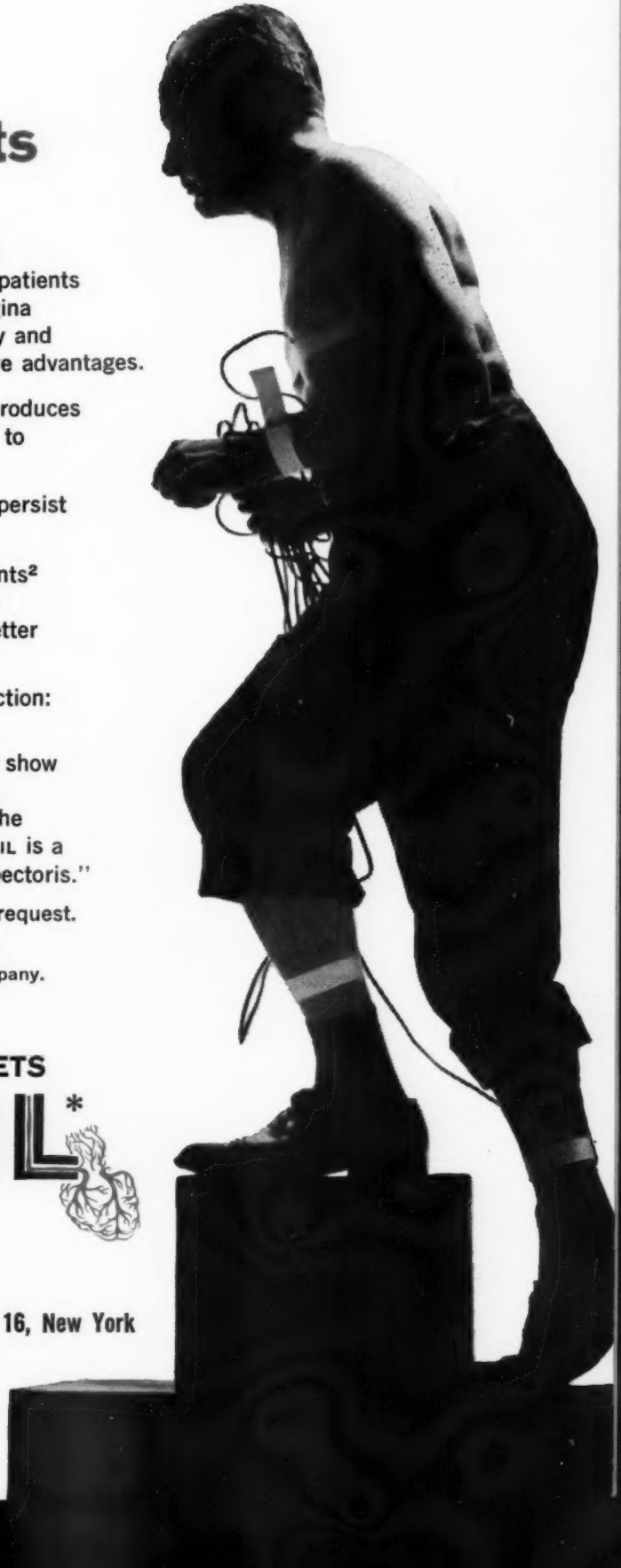

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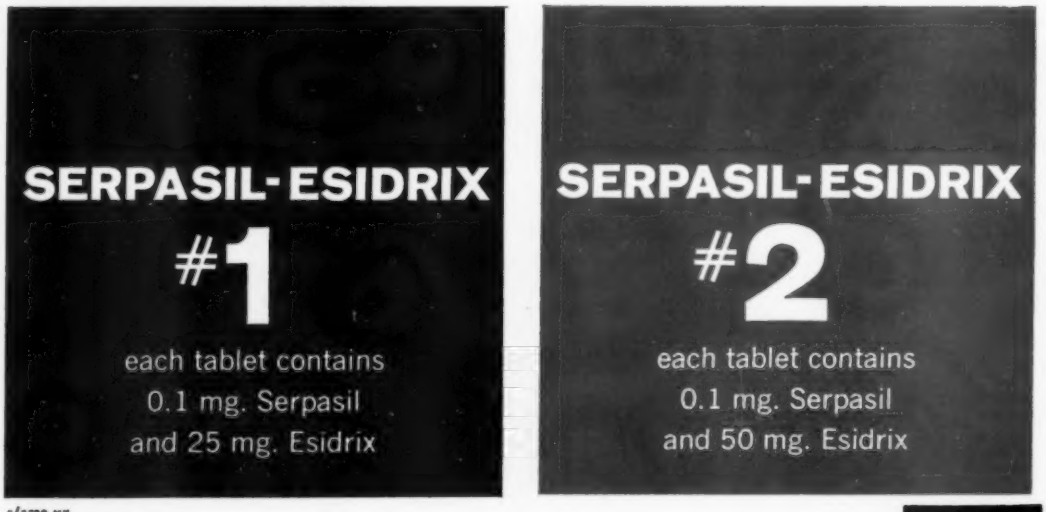

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THE FACTS ABOUT MER/29[1-41]

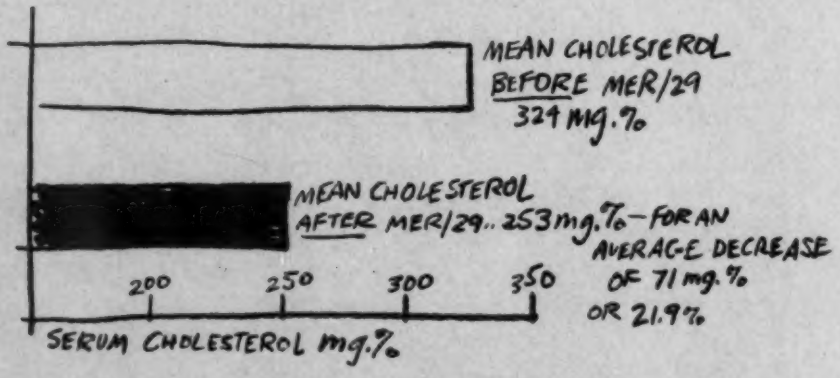
Fundamental differences between MER/29 and other cholesterol-lowering substances

Cholesterol produced within the body—its biosynthesis—is about three times as great as that obtained from dietary sources. Before MER/29, no method of modifying total body cholesterol production was known. Those measures used to lower cholesterol (unsaturated fatty acids or other dietary measures, vitamins, plant sterols, hormones, etc.) succeeded only in modifying exogenous sources of cholesterol or accelerating its metabolism.

MER/29 is fundamentally different, since it inhibits cholesterol biosynthesis. Thus, MER/29 offers for the first time a method of controlling total body cholesterol content.

MER/29 reduces serum cholesterol in 89% of patients, with or without dietary restrictions. Radioisotope studies indicate reduction of tissue cholesterol as well.[4, 5, 7, 30, 31, 34]

High cholesterol levels are generally considered those above 250 mg. %. Here is a tabular summary of preliminary data on MER/29 therapy in 463 patients with hypercholesterolemia (over 250 mg. %).



Clinical studies show that cholesterol reduction usually begins within two weeks. Maximum effect is achieved in five to eight weeks, and is maintained as long as therapy is continued. The studies of Hollander, Chobanian and Wilkins and those of Kountz found that cholesterol levels were lowered by MER/29 therapy irrespective of diet.

Reduction of total body "miscible pool" of cholesterol has been confirmed by radioisotope studies. Hollander and Chobanian, for example, found that the apparent miscible pool of cholesterol was reduced from 184 Gm. in the control period to 100 Gm. during MER/29 administration.

Studies in animals on MER/29 have shown the following tissue changes: erythrocyte cholesterol levels reduced 40%; plasma cholesterol reduced 62%; liver reduced 40%; skeletal muscle reduced 27%; lung reduced 33%; aorta reduced 21%. Significantly, brain and adipose tissue remained unaffected during the period of observation.

Safety and toxicity studies[5, 7, 10, 12, 17, 19, 21-24, 30, 32-34]

MER/29 is well tolerated. In a recent analysis of 576 individual case reports, 165 had been treated with MER/29 for continuous periods in excess of a year. A number had received two to four times the daily recommended dose for as long as 16 months. Side effects were seldom seen, and the incidence of those reported (nausea, dermatitis) was too low for positive correlation with administration of the drug.

In no case has there been clinical indication of toxic effects on the function of any vital organ or system. It should be noted that excretion of MER/29 or its metabolites may produce a false positive reaction for albuminuria.

THE FACTS ABOUT MER/29

Clinical observations of MER/29 in atherosclerosis[5, 7, 10, 12, 17-19, 21, 23-25, 28-34, 41]

The lowering of high cholesterol levels is regarded by many as a desirable clinical objective. Moreover, a substantial body of medical opinion implicates elevated cholesterol as a contributor to coronary artery disease and generalized atherosclerosis. Since MER/29 lowers total body cholesterol, can it modify atherosclerotic conditions? While the ultimate answer must await the results of long-term clinical experience, preliminary observations were reported at...

The MER/29 Conference at Princeton

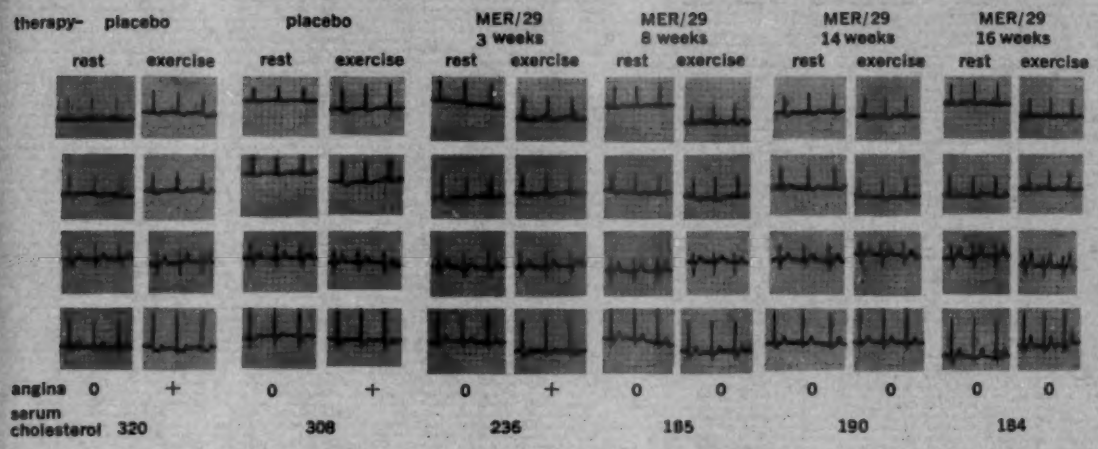
To help find the answer, 18 leading research teams met to discuss the relationship of MER/29 to cholesterol metabolism and atherosclerosis. The conference, moderated by Dr. Irving S. Wright, and summarized by Dr. Konrad E. Bloch, Dr. Robert W. Wilkins, and Dr. Irvine H. Page, was held last December at Princeton, New Jersey.

(The complete transcript of this conference is published as a supplement to the May, 1960, issue of Progress in Cardiovascular Diseases.)

Objective findings

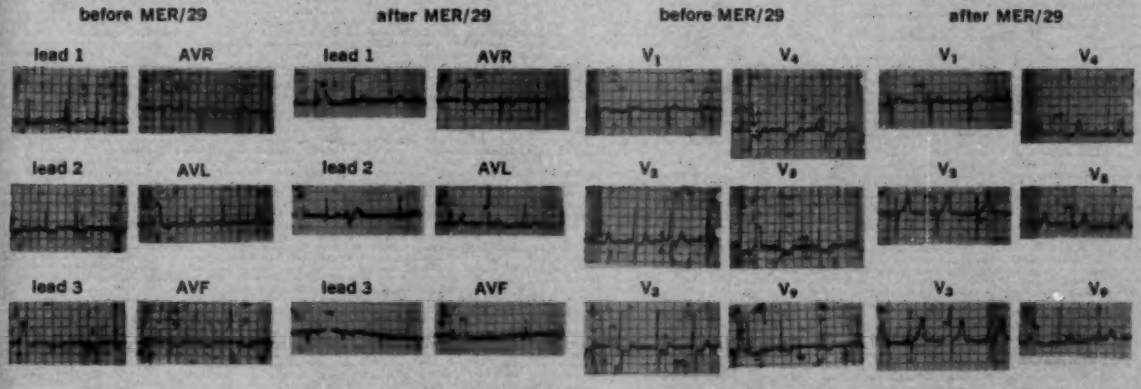
The team of Dr. William Hollander, Dr. Aram V. Chobanian, and Dr. Robert W. Wilkins at Massachusetts Memorial Hospitals, presented Fig. 1. It indicates a reversal of exercise-precipitated ECG abnormalities in a patient with angina pectoris during four months of MER/29 therapy. In all, they reported that three of nine patients showed reversal of exercise-induced ECG abnormalities after three months of MER/29 therapy.

fig. 1



Dr. Philip Lisan of Dr. John H. Moyer's group at Hahnemann Hospital presented Fig. 2. It also indicates reversal of ECG abnormalities in a patient with angina pectoris.

fig. 2



Dr. A. C. Corcoran of St. Vincent Charity Hospital, Cleveland, and Dr. Arthur Ruskin of University of Texas reported similar objective findings. All of these investigators noted that patients offered subjective evidence that they were experiencing a feeling of better health on MER/29 therapy, and that nitroglycerine dependence was diminishing.

Negative data were presented by Dr. Henry I. Russek of Staten Island, N. Y. He reported a study of exercise-electrocardiographic tests in 14 selected

subjects on MER/29. None of these patients had shown more than transient improvement in exercise tolerance after 3 months of treatment. It should perhaps be noted that this group of angina pectoris patients were a select group, having complained of symptoms for long periods of time.

Subjective findings

Dr. Meyer P. Halperin of Lynn, Massachusetts, reported a series of 18 patients with angina pectoris. Nine of this group obtained unequivocal subjective relief of symptoms after various periods of therapy with MER/29. An analysis of the duration of symptomatology in these patients indicated that response occurred more frequently when the ischemic heart disease had been present for shorter periods. Specifically, those who responded had had the condition for an average of 2.9 years, while the average time for those who did not respond was 5.2 years.

This study suggests that improvement in angina pectoris, when it occurs, may best be expected in those patients in whom the symptoms have been present for shorter periods of time. Additional experience will be required to determine whether long-term therapy can reverse long-standing symptomatology.

Dr. William B. Kountz of the Washington University School of Medicine, St. Louis, reported a group of 79 patients with varying degrees of hypertension, angina pectoris, diabetes, atherosclerosis or myocardial infarction. "Clinical improvement was observed and was also reported to us by patients. In some instances the anginal pain improved very much."

Similar subjective findings were also reported by

Dr. Corcoran, eight of whose nine patients noted a feeling of better health and increased exercise tolerance on MER/29. In three of these patients, nitroglycerine requirements were dramatically reduced.

IN SUMMARY ... MER/29 does consistently lower total body cholesterol by inhibition of endogenous cholesterol formation. Some patients with coronary artery disease, while on MER/29, have experienced concurrent clinical benefits such as reduction in frequency and severity of anginal attacks, reduction in nitroglycerine dependence, reversal of ECG abnormalities both at rest and following exercise-tolerance-induced changes, and an improved sense of good health and well-being.

The explanation of these clinical benefits is as yet unknown; however, several hypotheses have been advanced. One group speculates that MER/29 "may actually improve the adequacy of coronary circulation." Another investigator suggests that MER/29 exerts a vasodilating action, though pharmacologically MER/29 produces only transient vasodilating effects. Whatever the explanation, observation of these benefits among certain patients has awakened mounting interest in MER/29 as an important new agent in the management of patients with hypercholesterolemia and atherosclerosis.

MER/29 may be given to your patients with hypercholesterolemia and conditions thought to be associated with elevated cholesterol levels, including coronary artery disease (angina pectoris and postmyocardial infarction), and generalized atherosclerosis.

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Caution: MER/29 is a new drug which inhibits cholesterol biosynthesis in the body. Since cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

Hypercholesterolemia and its associated conditions may require MER/29 therapy over a long period. MER/29 has been shown to be entirely safe in the periods the drug has been studied, but long-term or lifetime effects are unknown. Periodic examination of patients on long-term MER/29 therapy is therefore necessary. While clinical liver damage has not been encountered, periodic liver function tests may be desirable until more long-term safety data are available.

Note: The specific site of action of MER/29 is now known to be between desmosterol (reported to be the last precursor in the synthesis path) and cholesterol. Although greater than normal quantities of desmosterol can be qualitatively shown in the livers and blood of animals and the blood of human beings treated with MER/29, reduction of total sterols suggests little, if any, accumulation. The significance of the presence of this substance is unknown and speculative.

Compatible with other cardiovascular therapies: MER/29 is not to be considered a substitute for measures ordinarily employed to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. However, MER/29 is compatible with measures used in these disorders, including anticoagulants, nitroglycerine, and PETN.

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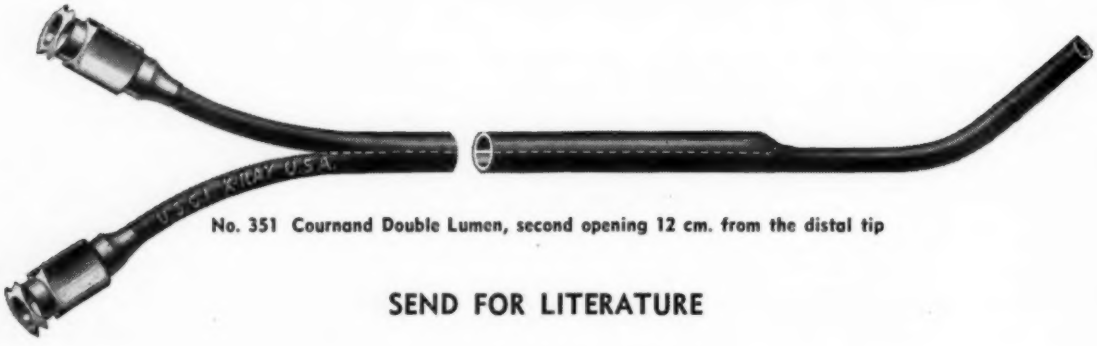

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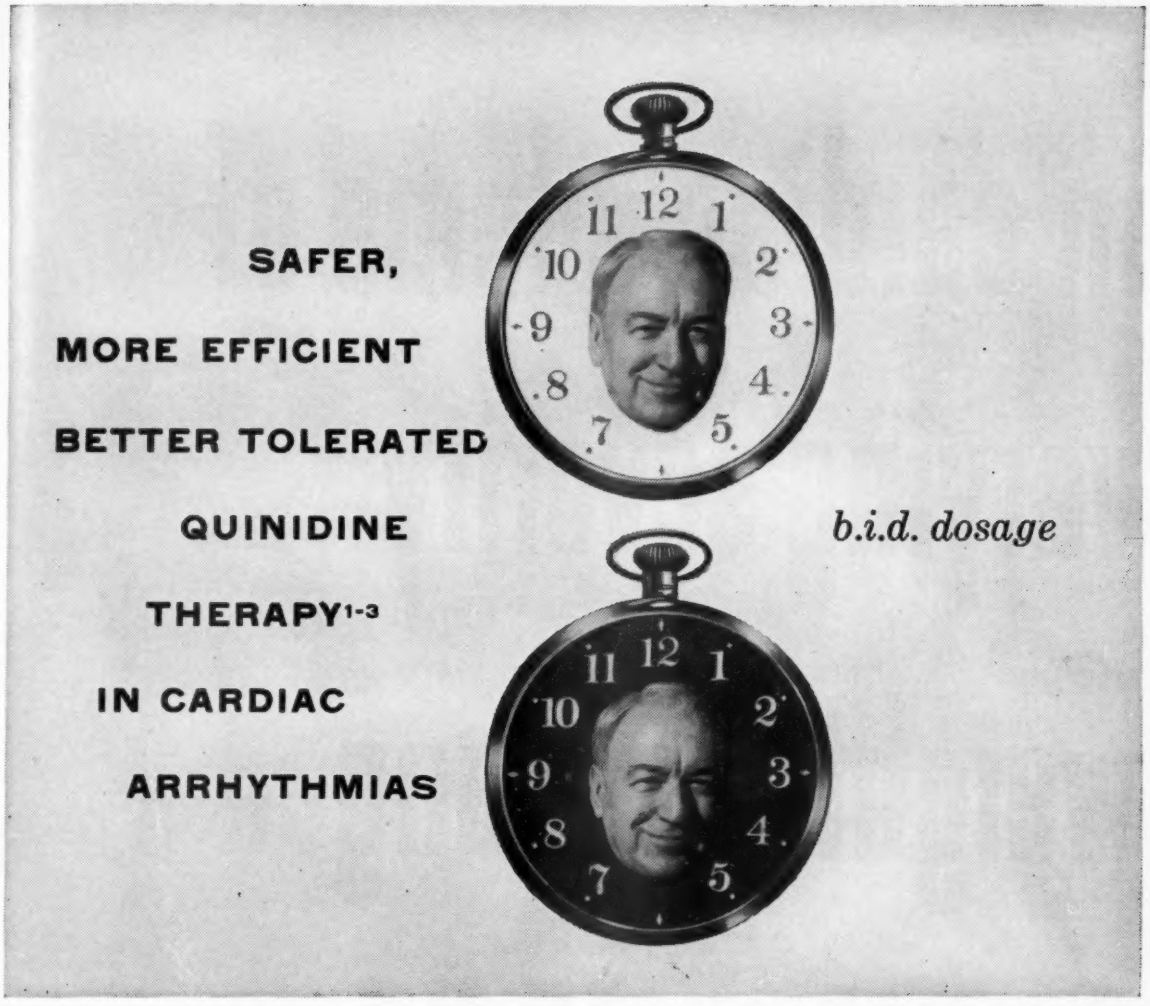

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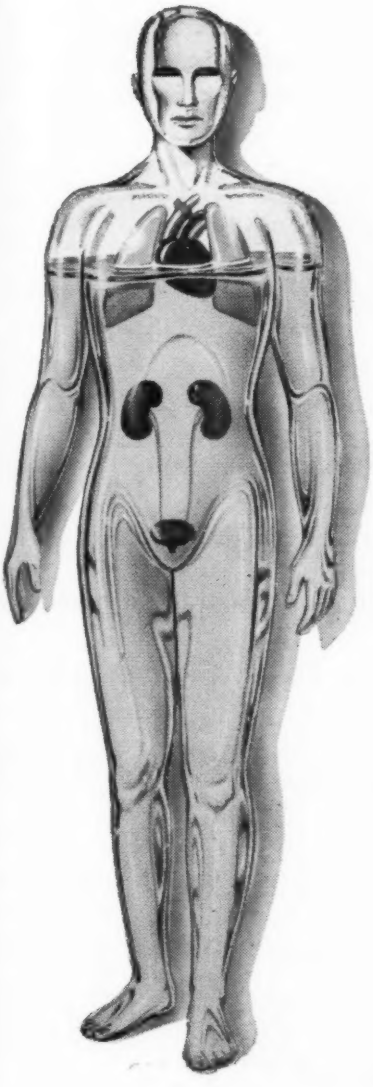

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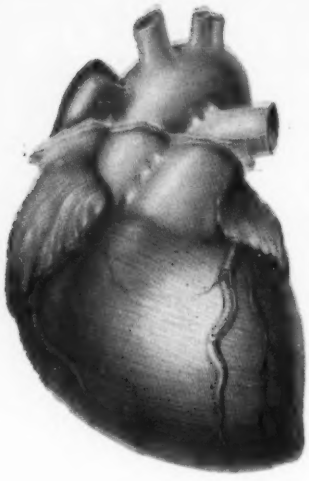

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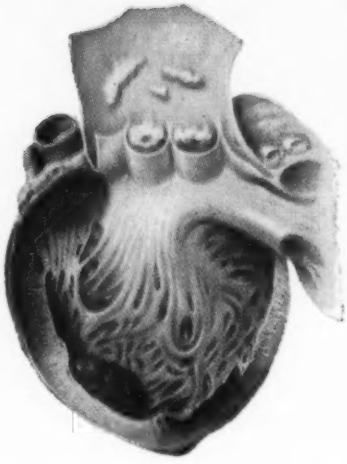

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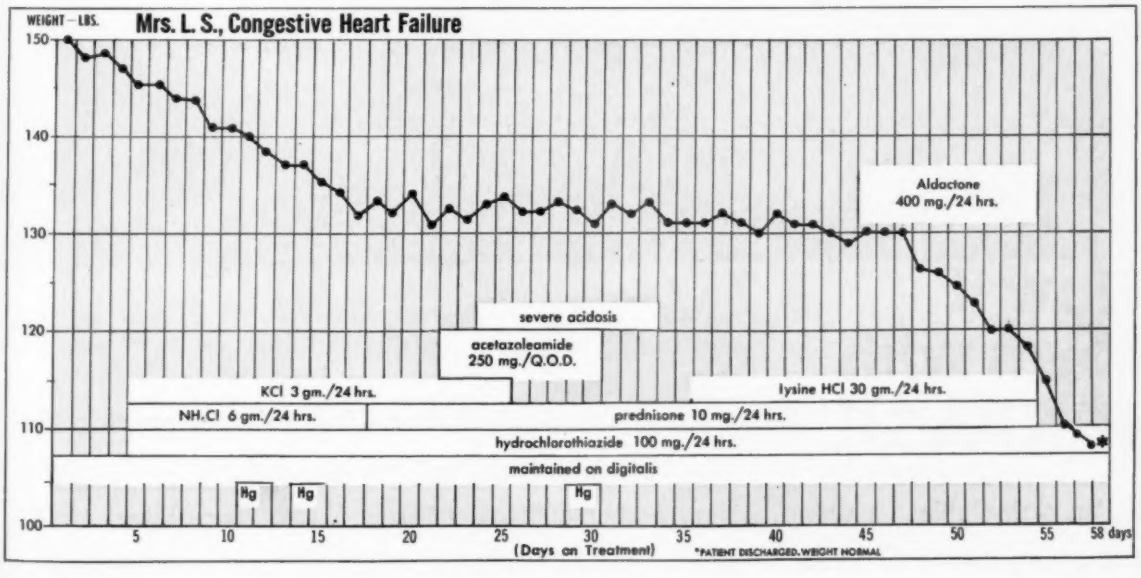

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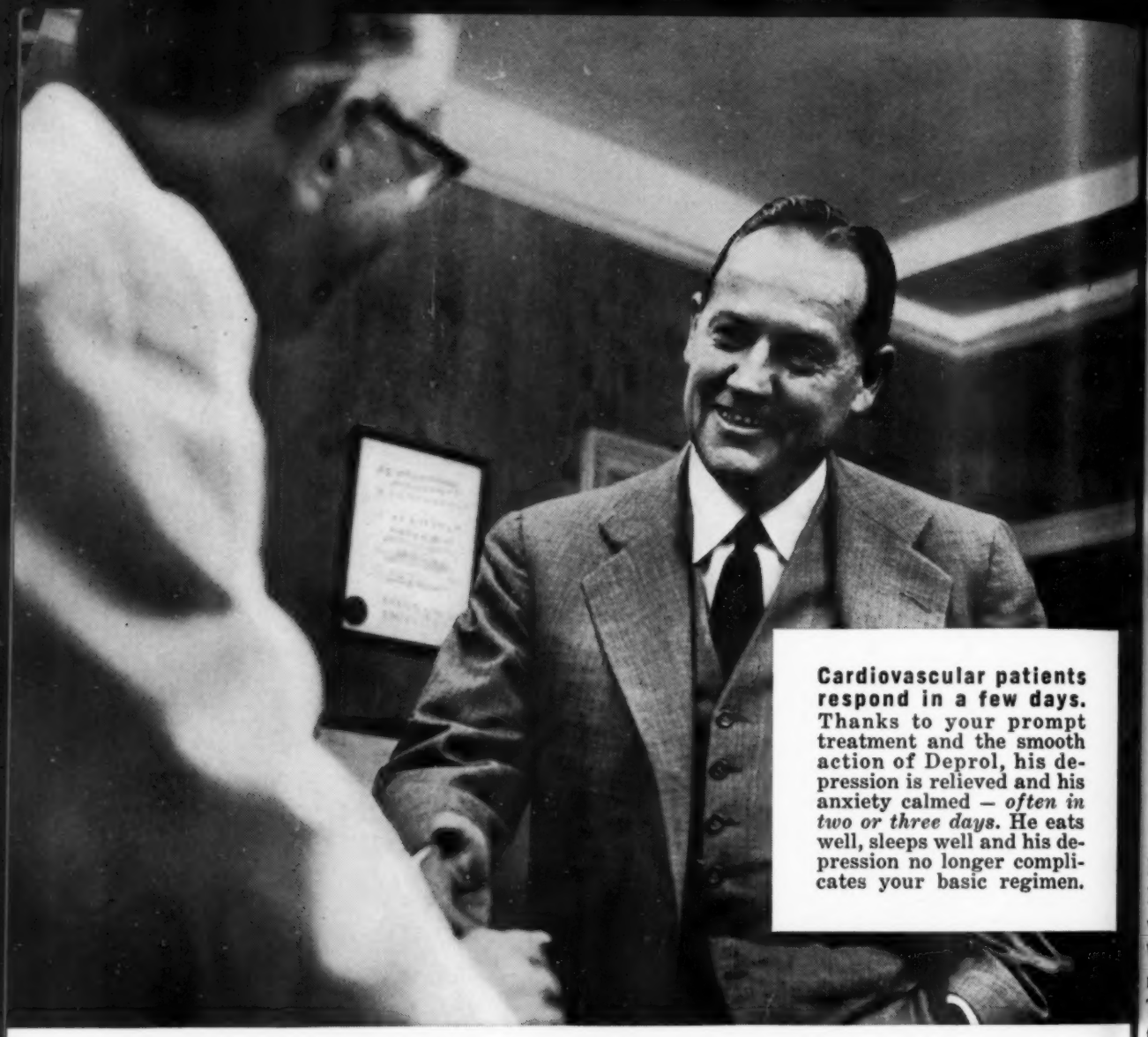

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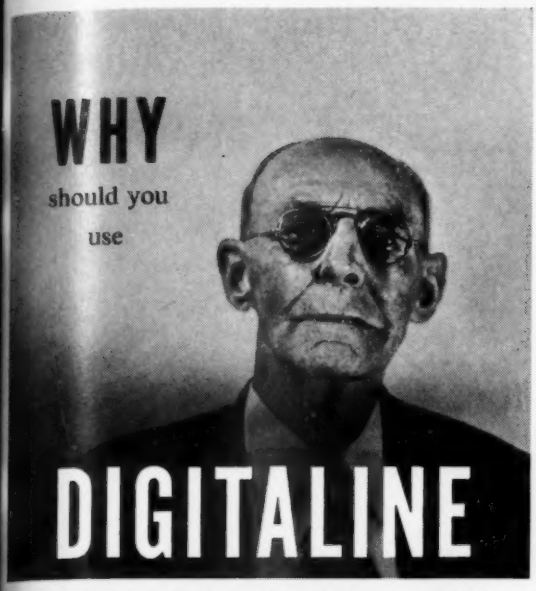

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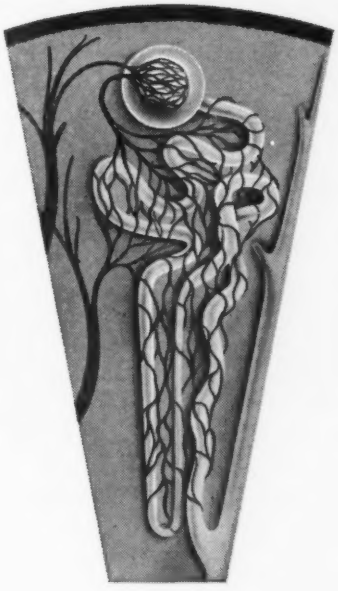

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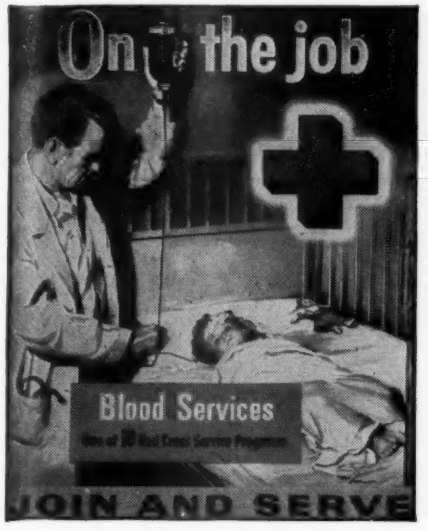

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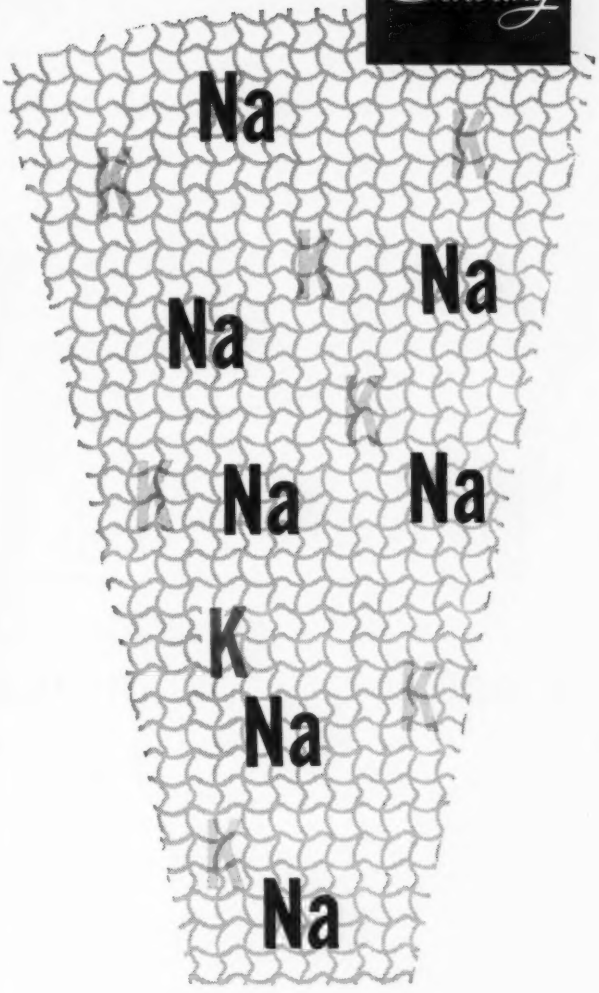

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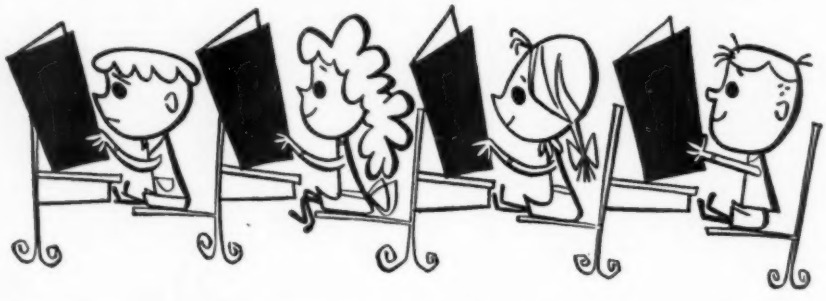

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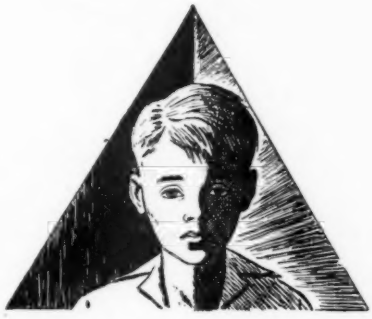

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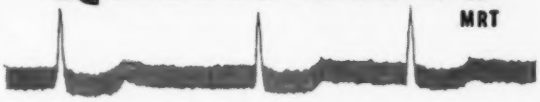

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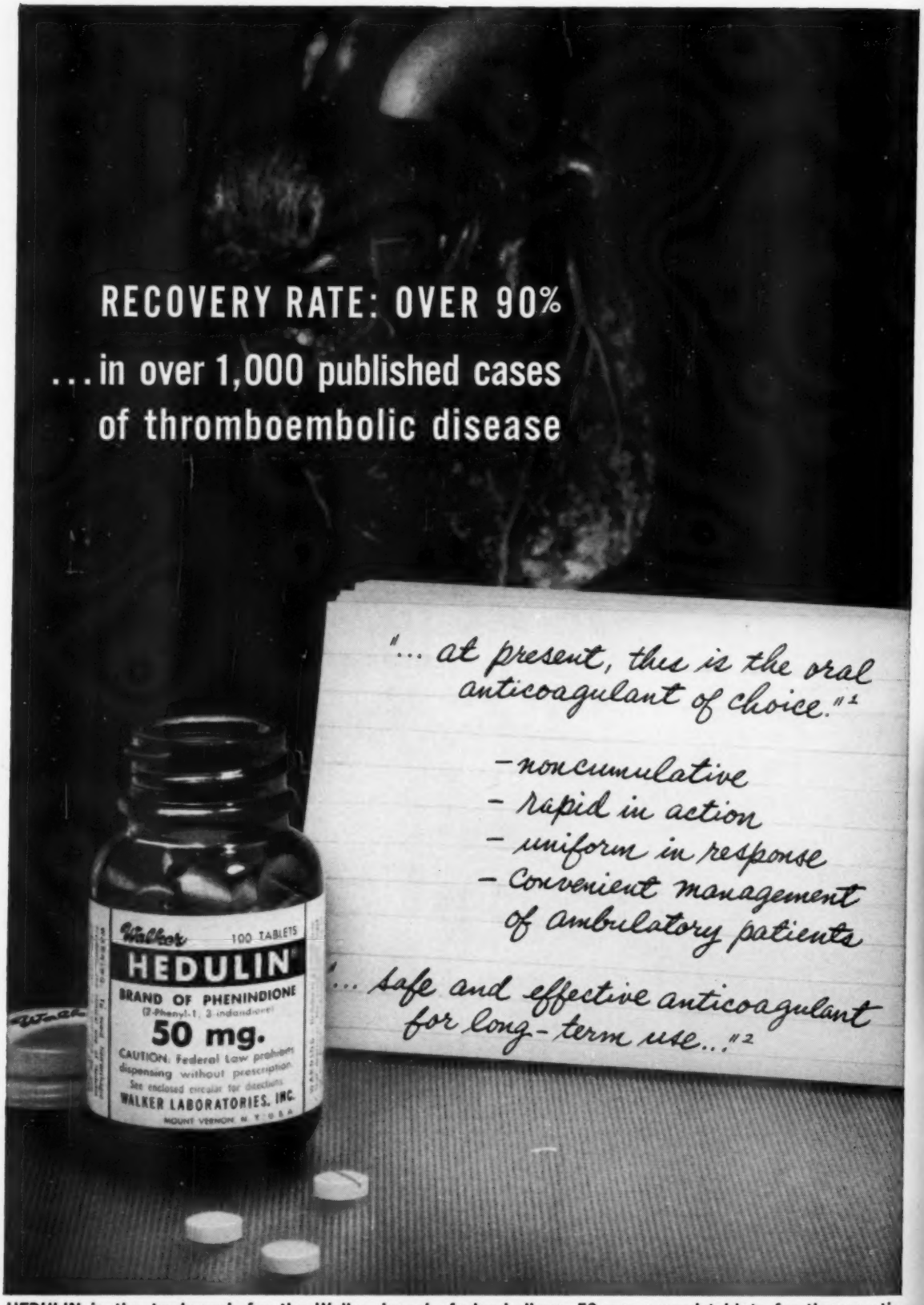
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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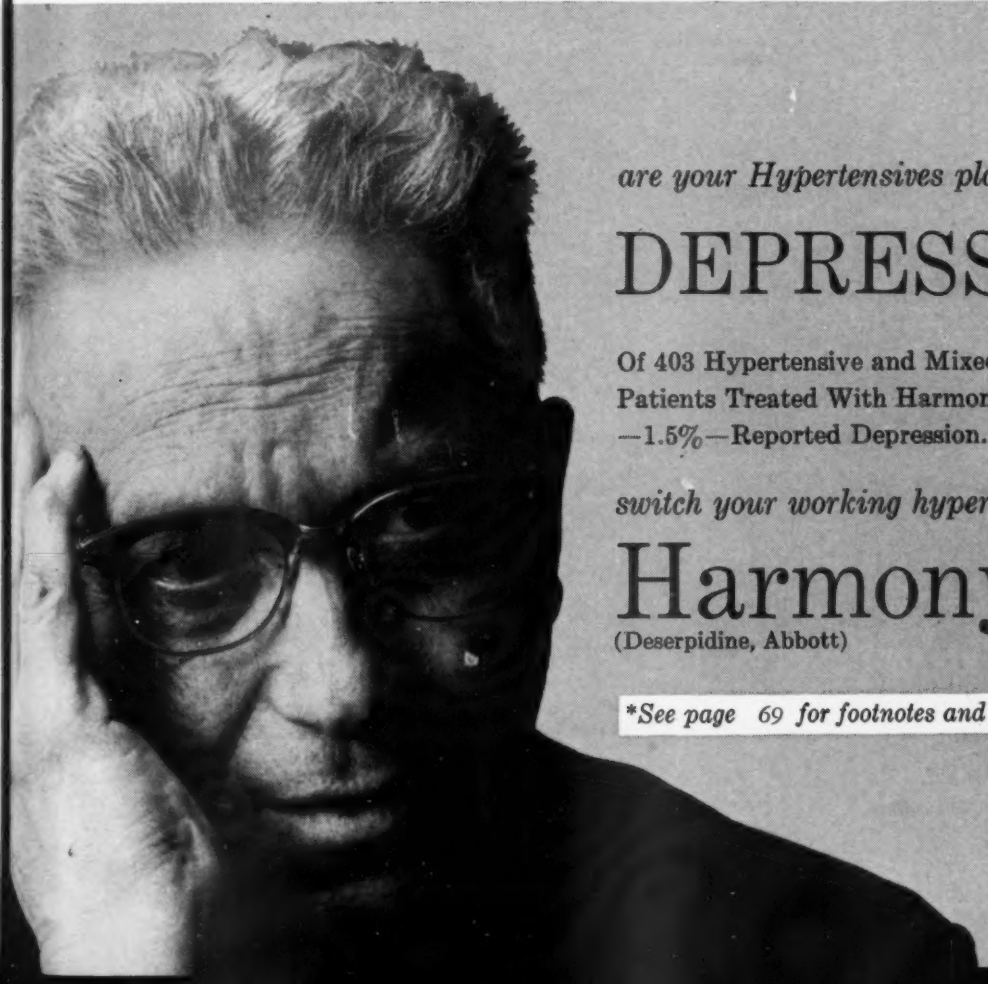

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Study #3. Forty patients with hypertension and anxiety neurosis . . . from mild to moderately severe. Half of the group had received other antihypertensive agents at one time or another; these were discontinued before and throughout the study. Usual dosage of Harmonyl was 0.1 mg. three times daily after meals. Sometimes an additional dose was taken at bedtime. No reports of depression associated with this therapy.[3]

Other investigators have found so little indication of depression with Harmonyl therapy that they do not record it as a significant side-effect.

1. Billow, B.W. et al., The Use of a New Rauwolfia Derivative, Deserpidine, in Mild Functional Disturbances and Office Psychiatry, N.Y. J. Med., 59:1789, May, 1959.
2. Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, 35:415, April, 1959.
3. Rawls, W.B. and Evans, W.L. Jr., Clinical Experiences with Deserpidine in the Management of Hypertension and Anxiety Neurosis, N.Y. J. Med., 59:1774, May, 1959.

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A DRUG THAT LOWERS CHOLESTEROL LEVELS AS MUCH AS 200 mg.%

WITH VIRTUALLY NO ANNOYING SIDE EFFECTS ...AND NO DIETARY RESTRICTIONS

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TABLETS aluminum nicotinate, Walker

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Dosage: 2 to 4 tablets t.i.d., with or after meals. Each tablet contains aluminum nicotinate (Walker) equivalent to 500 mg. of nicotinic acid.

Supplied: Bottles of 100 and 1000.

References: **1.** Tandowsky, R. M.: Personal communication. **2.** Parsons, W. B.: In press. **3.** Thompson, C. E.: Personal communication. **4.** Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. **5.** Hobbs, T. G.: Personal communication.

*PAT. PENDING

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1. Geriatrics, *12*:185, 1957.
2. J. Indiana M. A., *48*:603, 1955.

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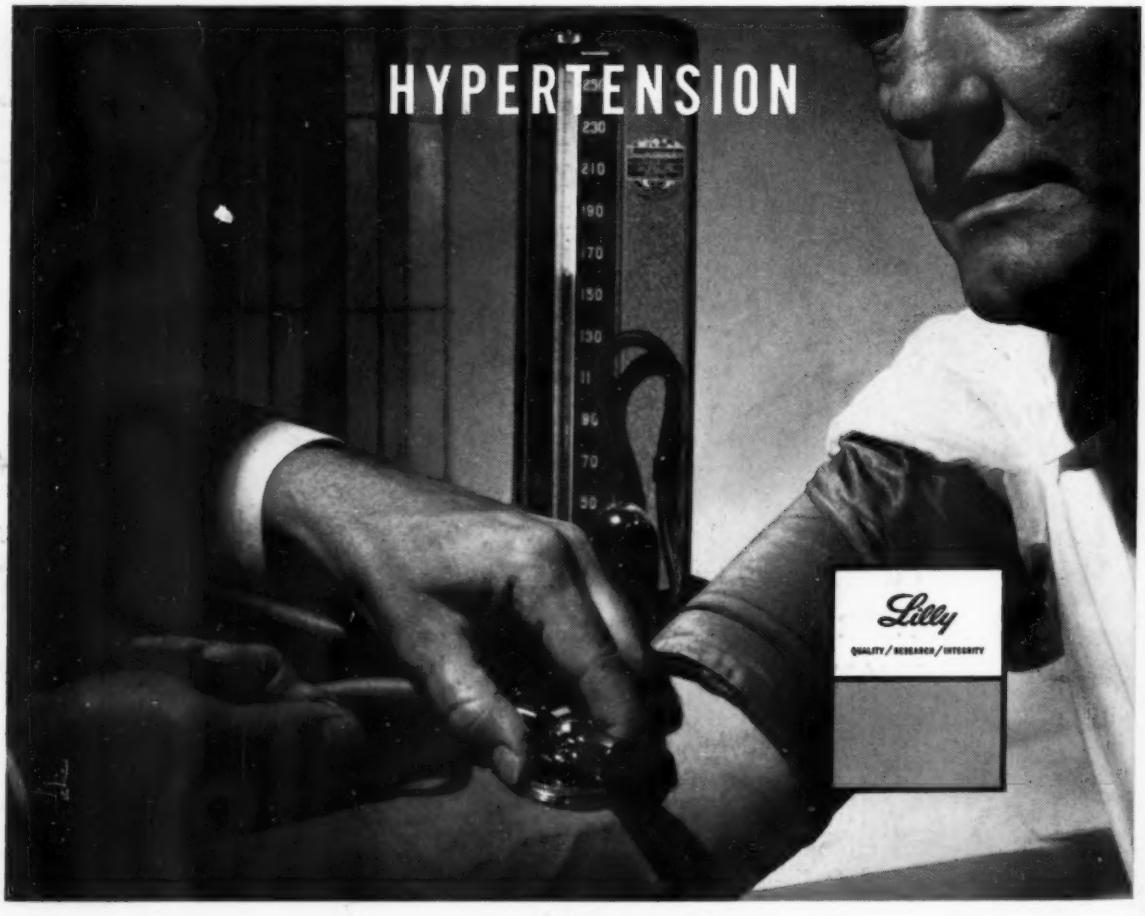

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